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EXPERIMENTS ON THE THEORY OF OSTEOGENESIS

THE INFLUENCE OF LOCAL CALCIUM DEPOSITS ON OSSIFICATION; THE OSTEOGENIC STIMULUS OF EPITHELIUM

C. B. HUGGINS, M.D.

H. R. McCARROLL, M.D.

AND

B. H. BLOCKSOM JR., M.D.

CHICAGO

Despite the numerous experimental data acquired especially since 1923, there are still defects in the knowledge of calcification in normal tissues, that is in calcified cartilage, teeth and bone. During this twelve year period, great advances in the subject have been made; much greater confidence is now held in the ideas of the state of calcium in the circulating blood and of the nature of the bone salts. Moreover, progress has been made in elucidating mechanisms by which transference is accomplished from the former, a liquid phase, to the solid phase found in calcified normal tissue. The importance of these mechanisms is obvious. It is elementary but axiomatic that improvements in knowledge of biologic mechanisms are reflected in improved clinical efficiency.

The purpose of the present communication is to indicate briefly some of the recent advances in this field and to present several experiments which perhaps integrate the subject further.

NATURE OF THE BONE SALT

The organic matrix of bone is little understood. As far as is known, it consists of the same collagen that is present in common connective tissue and cartilage,[1] together with an albuminoid and mucoid; the organic fraction contains a protein constituent with reducing characteristics, not precipitated by tri-chloracetic acid and soluble in acetone. Great advances have been made in understanding the nature of the inorganic bone salt, especially by the use of roentgen spectography. The principle of this method is that crystalline aggregates cause diffraction of roentgen rays, with the production of a spectrum typical for each

From the Department of Surgery of the University of Chicago.

1. Mörner, C. T.: Ztschr. f. physiol. Chem. **20**:237, 1895. Hawk, P. B., and Gies, W. J.: Am. J. Physiol. **5**:387, 1901.

crystalline molecular arrangement which is recordable on photographic film. The principle is the same as the diffraction grating, in which a series of finely drawn black lines on plate glass interfere with rays of visible light, causing them to be broken up into a spectrum.

De Jong [2] found in all specimens of bone examined, both ancient and modern, lines typical of the apatite group of calcium phosphate minerals; this means that calcium phosphate [$Ca_3(PO_4)_2$] and calcium carbonate [$CaCO_3$] are present as a double salt rather than as mixtures of calcium phosphate [$Ca_3(PO_4)_2$] and calcium carbonate [$CaCO_3$]. This work was confirmed [3] and extended by Roseberry, Hastings and Morse,[4] who found that most of the lines in both bone and teeth corresponded closely with the apatite mineral dahlite and that calcium carbonate [$CaCO_3$] does not exist in bone as such. J. H. Clark [5] showed that the apatite crystals in the shaft of a long bone have a tendency to longitudinal orientation, and she presented evidence that organic crystals (collagen) are present. G. L. Clark and Mrgudich [6] confirmed J. H. Clark's observation regarding the orientation of inorganic crystals along the surface of the long axis of the humerus of the rat and found that this tendency to long fiber orientation was not normally present in regions of bone where tendons or bony processes were attached or during the active and healed stages of rickets.

This idea that the inorganic salts of teeth and bone are similar to the apatite salts of nature is not new but was postulated by Hoppe [7] in 1862 on analytic grounds. Further evidence [8] obtained by stoichiometric methods supports this view. The formula for the inorganic salts of bone proposed by de Jong gives the most reasonable concept of the normal inorganic crystallites: $3\,Ca_3(PO_4)_2.CaX_2$ in which X_2 represents CO_3, O, Cl_2, F_2, $(OH)_2$, SO_4.

This formula may be regarded as adequately explaining the normal bone salts, but it does not indicate the quantitative amounts of the various apatite salts present which apparently depend on other factors. Morgulis [9] made a significant observation that in the bones of marine fishes the calcium phosphate [$Ca_3(PO_4)_2$]-calcium carbonate [$CaCO_3$] ratio is radically different from that in all other animals examined, and he logically accounted for the diminished amount of calcium car-

2. de Jong, W. F.: Rec. d. trav. chim. d. Pays-Bas **45**:445, 1926.

3. Taylor, N. W., and Sheard, C.: J. Biol. Chem. **81**:479, 1929.

4. Roseberry, H. H.; Hastings, A. B., and Morse, J. K.: J. Biol. Chem. **90**:395, 1931.

5. Clark, J. H.: Am. J. Physiol. **98**:328, 1931.

6. Clark, G. L., and Mrgudich, J. N.: Am. J. Physiol. **108**:74, 1934.

7. Hoppe, F.: Virchows Arch. f. path. Anat. **24**:13, 1862.

8. Gassmann, T.: Ztschr. f. physiol. Chem. **70**:161, 1910. Bogert, L. J., and Hastings, A. B.: J. Biol. Chem. **94**:473, 1931.

9. Morgulis, S.: J. Biol. Chem. **93**:455, 1931.

bonate by referring it to the low plasma bicarbonate concentration of the blood in these species. As Morgulis pointed out, this observation militated against the view that the carbonate apatite is the principal crystallite deposited in normal tissues. The distribution of the apatites in the bone of the fish seemingly is dependent on the constitution of the circulating blood, and presumably larger amounts of oxyapatite and hydroxyapatite are present in fishes than in mammals, in which the high plasma bicarbonate accounts for carbonate apatite deposits.

The blood serum under abnormal conditions similarly affects the mineral composition of bone. While normally the principal cations present are calcium and magnesium, in poisoning others, such as the salts of lead, strontium, silver, radium and related salts, like thorium,[10] form in bone, reflecting their presence in the blood stream. Moreover insoluble lakes such as are formed between alizarate and calcium accumulate in bone when they are present in the blood stream. There is another class of substances which from their chemical behavior throw light on the deposition mechanism, that is, the accumulations of urates in bone in gout. In this case the cation is soluble and the anion very slightly soluble at physiologic hydrogen ion concentrations in the tissues, and nevertheless the urate accumulates at certain areas in bone.

The conclusion, then, is that the inorganic constitution of bone is influenced by the composition of the body fluids, and under normal conditions the predominant salts are of the apatite group, which may be expressed by the formula of de Jong, but that under abnormal conditions other salts accumulate and that any chemical combination which tends to make an insoluble or difficultly soluble salt in a faintly alkaline watery medium will be found in bone and teeth.

THE STATE OF CALCIUM IN THE BODY FLUIDS

Using a biologic method which depended on the sensitivity of the heart of the frog for calcium ions, McLean and Hastings [11] discovered that total calcium, total protein and calcium bound to protein are all interrelated in an equilibrium which as a first approximation can be represented by a simple mass law equation. In other words, the amount of ionized calcium is greatly influenced by the protein concentration of plasma.

MECHANISM OF DEPOSITION OF APATITE SALTS IN CARTILAGE

Significant data have been accumulated on the deposition of apatite salts in cartilage, especially on calcification in vitro. Shipley [12] made

10. Behrens, B., and Baumann, A.: Ztschr. f. d. ges. exper. Med. **92**:251, 1933.

11. McLean, F. C., and Hastings, A. B.: Proc. Soc. Exper. Biol. & Med. **30**:1344, 1933; **31**:529, 1934.

12. Shipley, P. G.: Bull. Johns Hopkins Hosp. **35**:304, 1924.

the important observation that calcification of epiphyseal cartilage in rickets took place in normal serum but not in rachitic serum; Robison and Soames [13] and Shipley, Kramer and Howland [14] found that it similarly occurred in artificial fluids in vitro. The calcification is analogous to spontaneous healing in rickets and takes place in the presence of adequate calcium and phosphorus ions, at an appropriate p_H at body temperature. It does not occur [14] in the icebox and is inhibited by a number of factors, such as soaking in chloroform, ether or solution of formaldehyde, the presence of magnesium ions,[15] an increase of total ions in solution,[16] the presence of dextrose [17] and heating to a temperature of 60 C. for ten minutes.

It was by the use of rachitic cartilage in vitro as an indicator that Robison proved the presence of the monophosphoric esterase, phosphatase, in calcifying cartilage.[18] Robison pointed out that there were two mechanisms involved in the formation of rachitic epiphyseal cartilage: (1) the monophosphoric esterase and (2) a mechanism concerned with local deposition from a supersaturated solution in the selective way that occurs in healing rachitic cartilage in vivo, crudely expressed as "the line test."

An important advance recently achieved by Robison and Rosenheim [17] was the successful deposition of a line of strontium in rachitic epiphyseal cartilage in vitro from an inorganic solution in which strontium replaced the calcium ions. This is experimental evidence that the deposition from inorganic solutions is not a specific effect of calcium and further that any difficultly soluble salt in a faintly alkaline medium is biologically precipitable as a bone salt.

MECHANISM OF PRECIPITATION OF INORGANIC SALTS IN BONE

Beyond the fact that bone contains a phosphoric esterase [18b] in large amount, even at a bone age of less than 24 hours,[19] nothing is known about the mechanism of calcification in mammalian bone. However, Fell and Robison [20] successfully cultivated in vitro the isolated femur

13. Robison, R., and Soames, K. M.: Biochem. J. **18**:740, 1924.

14. Shipley, P. G.; Kramer, B., and Howland, J.: Biochem. J. **20**:379, 1926.

15. Shipley, P. G., and Holt, L. E.: Bull. Johns Hopkins Hosp. **41**:437, 1927. Kramer, B.; Shelling, D. H., and Orent, E. R.: ibid. **41**:426, 1927. Robison, R.; MacLeod, M., and Rosenheim, A. H.: Biochem. J. **24**:1927, 1930.

16. Shelling, D. H.; Kramer, B., and Orent, E. R.: J. Biol. Chem. **77**:157, 1928.

17. Robison, R., and Rosenheim, A. H.: Biochem. J. **28**:684, 1934.

18. Robison, R.: (*a*) Biochem. J. **17**:286, 1923; (*b*) The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932.

19. Huggins, C. B.: Biochem. J. **25**:728, 1931.

20. Fell, H. B., and Robison, R.: Biochem. J. **23**:767, 1929.

from 5½ and 6 day fowl embryos, and bone formed in their tissue cultures; the phosphatase content was low at the time of explantation and increased greatly at the time of calcification. The mechanism of calcification in bone differs appreciably from that of calcification of hypertrophic cartilage in that, as stated, cartilage calcifies in vitro under favorable conditions whereas osteoid does not calcify under the conditions which are effective for calcification of cartilage.

The question whether the osteoblast is or is not a specific type of cell endowed with specific functional characteristics seems to be settled in the affirmative. The opinion most recently stated by Jones and Roberts,[21] and previously advocated by LeRiche and Policard,[22] that the osteoblast cannot be regarded as a cell endowed with the specific power of laying down bone and that the bone cell is a fibroblast imprisoned in bone in a state of quiescence, can easily be shown to be erroneous, and further data in this regard will be presented later. The evidence shows that the osteoblast is derived from cells of the fibroblast series and that it differs from its precursors, although more from a physiologic than from an anatomic standpoint.

It was shown [23] in the dog that ossification occurs readily in certain fibroblast areas under the influence of the epithelium of the urinary tract. These observations derived from surgical methods have been confirmed by several groups of workers.[24] The mechanism by which epithelial cells influence certain fibroblasts to produce bone is unknown; except for phosphatase determinations [25] and the failure of an extract of bladder mucosa to form bone,[24b] no chemical facts are known about this effect, which is still in a descriptive physiologic state. A similar effect has been found in the mucosa of the gallbladder in the dog and the guinea-pig [26] and in germ elements of teeth.[27]

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21. Jones, R. Watson, and Roberts, R. E.: Brit. J. Surg. **21**:461, 1934.

22. LeRiche, R., and Policard, A.: The Normal and Pathological Physiology of Bone, translated by S. Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

23. Huggins, C. B.: (*a*) Proc. Soc. Exper. Biol. & Med. **27**:349, 1930; (*b*) The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, Arch. Surg. **22**:377 (March) 1931.

24. (*a*) Abbott, A. C., and Goodwin, A. M.: Canad. M. A. J. **26**:393, 1932. (*b*) Copher, G.; Key, J. A., and West, E. S.: Proc. Soc. Exper. Biol. & Med. **29**:646, 1932. (*c*) Roome, N. W., and McMaster, P. E.: Influence of Venous Stasis on Heterotopic Formation of Bone, Arch. Surg. **29**:54 (July) 1932. (*d*) Regen, E. M., and Wilkins, W. E.: J. Lab. & Clin. Med. **20**:250, 1934. (*e*) LeRiche, R., and Lucinesco, E.: Presse méd. **43**:137, 1935. (*f*) Jung, A., and Cemil, S.: ibid. **43**:140, 1935.

25. Huggins.[19] Regen.[24d]

26. Huggins, C. B., and Sammett, J. F.: J. Exper. Med. **58**:393, 1933.

27. Huggins, C. B.; McCarroll, H. R., and Dahlberg, A. A.: J. Exper. Med. **60**:199, 1934.

The present experiments were concerned with two questions: (1) whether a local calcium deposition stimulates osteogenesis and (2) the nature of the epithelial osteogenetic stimulus.

THE INFLUENCE OF LOCAL CALCIUM DEPOSITS ON OSSIFICATION

The evaluation of the importance of a local calcium deposit as an osteogenetic stimulus is difficult. It seems plain that the solid phase of the bone salt facilitates further deposition from a supersaturated solution of calcium with phosphate and other anions concerned in apatite formations. From a biologic standpoint, formation of bone adjacent to calcified tubercles, fibroids, atheromatous plaques and renal calculi [28] is not an uncommon observation. Moreover, the presence of bone salt deposition in the scaffolding of calcified cartilage in bones which pass through a chondral stage apparently facilitates replacement of the cartilage by bone, but in what manner this takes place it is impossible to say at present. Since bone forms in the skull and clavicle without a calcified precursor, it is known that a calcified deposit is not an absolute prerequisite. From an experimental standpoint, calcium salts have apparently led to formation of bone in two instances. Barth [29] implanted ashed bone in the peritoneal cavity of the cat and observed new formation of bone closely adjacent. Similarly, Wurm [30] observed bone three months after implantation of a calcium phosphate-calcium carbonate mixture in young rabbits, after completely negative results had been observed in older animals.

These experimental observations showing that bone has formed away from the skeleton, however, have not been confirmed by the experience of most workers, notably Morpurgo and Martini, Liek, Pochhammer, Rhode and others.[31] The issue is somewhat clouded by the results of experimental implantation of calcium salts in an artificial bone defect, since it is difficult to tell how much new formation of bone arises from the original skeletal elements growing along and through the implanted inorganic salts and how much arises from direct action of these salts on nonskeletal fibroblasts. Thus Albee and Morrison,[32] Murray,[33] Cretin [34] and others expressed the belief that inorganic salts facilitate the healing of artificially created bone defects. On the other hand,

28. Huggins, C. B.: Bone and Calculi in the Collecting Tubules of the Kidney, Arch. Surg. **27**:203 (July) 1933. Phemister, D. B.: Ann. Surg. **78**:239, 1923.

29. Barth, A., cited by Wurm.[31]

30. Wurm: Verhandl. d. deutsch. path. Gesellsch. **25**:191, 1930.

31. Cited by Wurm, H.: Beitr. z. path. Anat. u. z. allg. Path. **85**:401, 1930.

32. Albee, F. H., and Morrison, H. F.: Ann. Surg. **71**:32, 1920.

33. Murray, C. R.: J. Dent. Research **11**:837, 1931.

34. Cretin, A., cited by Haldeman and Moore.[37]

Eden,[35] Key,[36] Haldeman and Moore [37] and Brunschwig and Harmon,[38] representing a majority of the investigators in this field, reported that the solid bone salts have no or slight influence on the production of new bone. Furthermore, as pointed out by Brunschwig and Harmon,[39] the fact that certain skeletal tumors ossify together with all metastases strongly indicates the presence of a specific cell type, the osteoblast.

EXPERIMENTAL DATA

EXPERIMENT 1.—*Implantation of bone salts in abdominal wall, surgical defect in rib and trephine defect in skull.*

Method.—The femur and skull of a 1 year old dog were sawed into segments 2 cm. in length, and these were boiled in a 5 per cent solution of potassium hydroxide for three days, the alkali being changed repeatedly, until the organic framework was completely hydrolyzed. The completeness of hydrolysis was determined by the absence of nitrogen as determined by the Kjeldahl method. The masses of bone were then washed for two days in running water until they exhibited a neutral reaction; then they were sterilized in an autoclave.

With the animal under ether anesthesia, aseptic precautions being used, this deproteinized bone was implanted (1) between the external oblique and the internal oblique muscle of the abdomen in twelve dogs; (2) in a 2 cm. defect following subperiosteal costectomy in six dogs; (3) in a defect produced by a crown trephine in the parietal bone of the skull in six dogs. The wounds were closed with fine silk. The animals were killed at two week periods, beginning two weeks after operation.

Results: 1. Implantation of deproteinized bone into the abdominal wall did not lead to new formation of bone in any instance; the implant was gradually absorbed. In the two week specimen many of the channels which had contained blood vessels before alkaline hydrolysis were already filled with new blood vessels. The inorganic salts had become infiltrated with protein, so that after decalcification of the specimen by hydrochloric acid a protein framework was left. The osteocyte spaces were not infiltrated by cells. The mass was surrounded by a capsule of fibrous tissue. Noteworthy was the absence of giant cells.

Specimens examined four, six and eight weeks after implantation showed similar features; it was difficult to prove absorption of the inorganic salts up to this time, although it was believed that it had occurred. In specimens examined ten, twelve and fourteen weeks after implantation the absorptive process was clearly seen; there had occurred fragmentation of the bone salt implants. After sixteen and eighteen weeks only traces of the implants were detectable.

2. Implantation in a costal defect led to encapsulation of the inorganic salt mass by fibrous connective tissue, with partial extrusion of the mass out of contact with the rib and partial resorption in each case. No sign of formation of new bone was observed.

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35. Eden, R.: Klin. Wchnschr. **2**:1798, 1923.

36. Key, J. A.: J. Bone & Joint Surg. **16**:176, 1934.

37. Haldeman, K. O., and Moore, J. M.: Influence of Local Excess of Calcium and Phosphorus on the Healing of Fractures: An Experimental Study, Arch. Surg. **29**:385 (Sept.) 1934.

38. Brunschwig, A., and Harmon, P. H.: Am. J. Cancer **22**:342, 1934.

39. Brunschwig, A., and Harmon, P. H.: Surg., Gynec. & Obst. **57**:711, 1933.

3. Implantation of inorganic salts in the skull led to a slightly different result, in that in specimens examined four, six and eight weeks after implantation the new processes of bone which formed at the cut margins of the trephine defect were observed growing over the implant, and in several instances appositional replacement [40] occurred.

Comment.—The conclusion was reached that apatite implants of bone did not stimulate the connective tissue of the abdominal wall to form bone in the length of time in which these implants were present before

Fig. 1.—Section (× 30) showing transplant of deciduous tooth to abdominal muscles in a dog, sixty-three days after operation. New bone formation is shown in the fibroblasts filling the pulp canal.

complete absorption took place. The absence of giant cells during the resorptive process was a noteworthy feature.

EXPERIMENT 2.—*New formation of bone by transplantation of teeth to the abdominal wall.*

Method.—In ten young dogs between 6 and 9 weeks of age under ether anesthesia the deciduous canine tooth was painted with tincture of iodine and ampu-

40. Barth, A.: Arch. f. klin. Chir. **46**:409, 1893. Marchand, F.: Der Process der Wundheilung, Stuttgart, Ferdinand Enke, 1901.

tated with a hollow rongeur, at a point about 3 mm. distal to the margin of the gum. It was found that with practice this could be done without splintering the tooth. Maintaining this distance from the margin of the gum without splintering the tooth assured the absence of bone cells in the transplant. In four anesthetized pups of the same age an incision was made in the mucosa overlying the permanent unerupted canine tooth; this was exposed, the membranes were opened, and the tooth was extracted. In both the permanent and the deciduous teeth the pulp was gently lifted out and discarded. At least two teeth of each dog were thus obtained, and one of the pair was boiled for ten minutes in water to assure death

Fig. 2.—Higher magnification (× 250) of the section presented in figure 1, showing a portion of the pulp canal, with creeping substitution of dentin at *A*.

of the cells. The teeth were implanted in the abdominal wall, between the internal and the external oblique muscle. The specimens were recovered between thirty-five and sixty-three days after implantation.

Results.—1. Implantation of Normal Deciduous Teeth: In each case fibrous connective tissue was found filling the pulp space of the tooth, and always new bone was found, usually in this tissue (fig. 1), but in four teeth there was no ossification in the pulp space. In every case there was found oppositional substitution of the dentin by bone (fig. 2). The tooth was encapsulated by fibrous connective tissue. In two teeth infection was present, and in these teeth the amount of new bone was small.

2. Implantation of Boiled Deciduous Teeth: A similar encapsulation of the tooth and filling in of the pulp cavity with newly formed connective tissue were found. In every case there was complete absence of bone (fig. 3), although unboiled teeth from the same animal constantly contained deposits of new bone. In these implants of deciduous teeth the enamel was apparently undisturbed by resorptive changes which affected the dentin.

3. Implantation of Unboiled Unerupted Teeth: In this experiment bone was found in the pulp space in seven of ten teeth imp'anted in the abdominal wall,

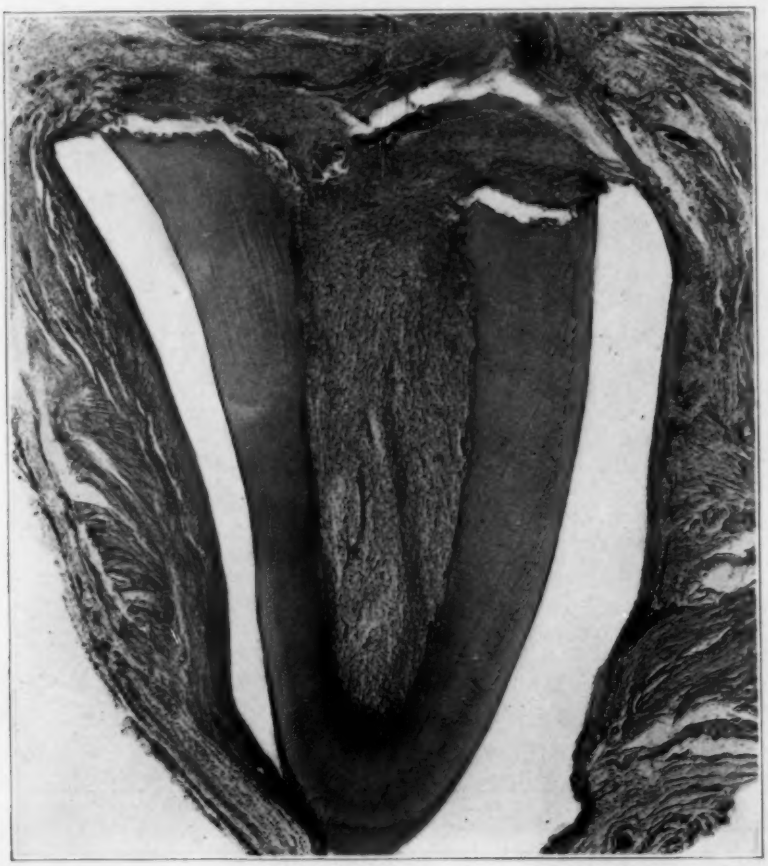

Fig. 3.—Section (× 30) showing transplant of a boiled deciduous tooth to abdominal muscles, sixty-three days after operation. No bone formation is present.

although it was less in amount than in the deciduous teeth. In three cases an interesting creeping substitution of the enamel occurred (fig. 4).

Comment.—This experiment is interpretable from two obvious standpoints. Either the apatite salts of tooth which are identical with the inorganic bone salt [4] act as a local stimulus to fibroblasts, or tooth cells are carried over in the transplantation and form bone. Since

boiling in water does not affect the inorganic salts and since it abolishes the formation of bone, it appears reasonable to ascribe the new bone to transplanted tooth cells rather than to the solid calcified phase.

The formation of bone in dental pulp tissue has been observed not infrequently,[41] after retention in the jaw of an unerupted tooth, fracture of a tooth, reimplantation, infection, etc. The bone has also been

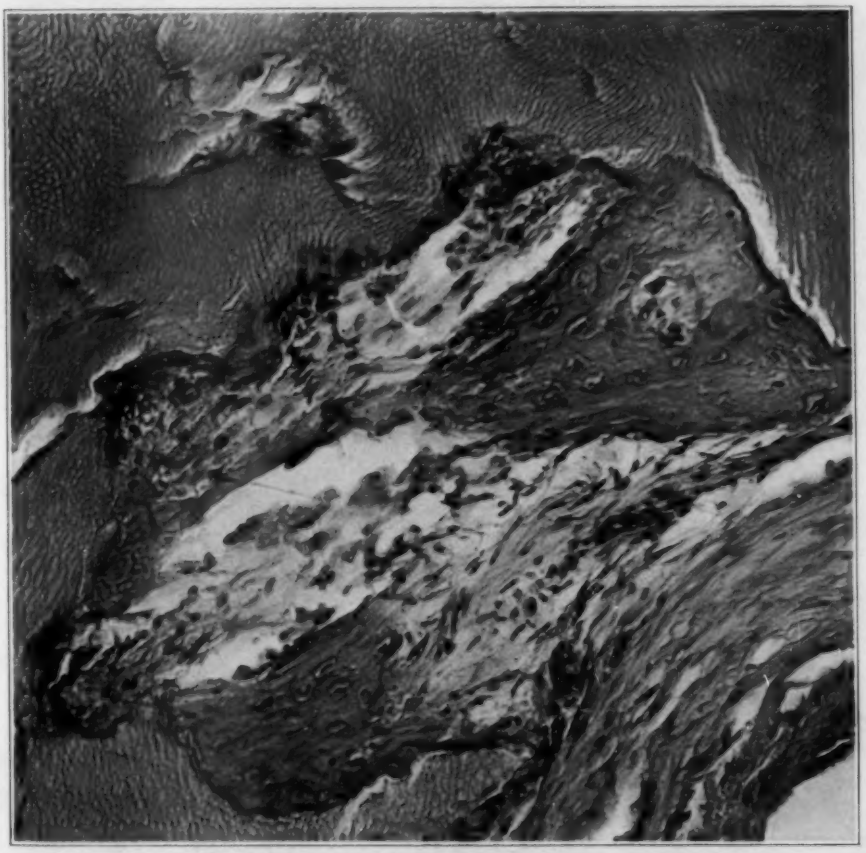

Fig. 4.—Section (× 250) showing creeping substitution of enamel by bone in an unerupted permanent tooth transplanted to the abdominal wall, after thirty-eight days.

41. Zuckerkandl, E.: Med. Jahrb., 1885, p. 1. Römer, O., in Henke, F., and Lubarsch, O.: Handbuch der speciellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 4, pt. 2, p. 309. Coolidge, E. D.: J. Am. Dent. A. **16**:821, 1929; **15**:1623, 1928. Worman, H. C.: ibid. **16**:1885, 1929. Willman, W.: ibid. **17**:444, 1930. Boulger, E. P.: ibid. **18**:988, 1931.

described as invading dentin and enamel in the fashion known as creeping substitution. Höjer [42] and Wolbach and Howe [43] similarly noted formation of bone (osteodentin) in the pulp in cases of vitamin C and vitamin A deficiency, which shows that under this abnormal circumstance the odontoblasts lose histologic polarity and act as osteoblasts.

Fig. 5.—Roentgenogram of a spleen in which four pieces of epithelium of the urinary bladder had been transplanted in the upper two thirds with no bone formation, while in the lower pole, where epithelium and sheath of the rectus abdominis muscle were transplanted together, bone was formed at fifty-seven days. The arrow points to the bone density.

42. Höjer, J. A.: Acta pædiat. (supp.) **3**:8, 1924.
43. Wolbach, S. B., and Howe, P. R.: Am. J. Path. **9**:275, 1933.

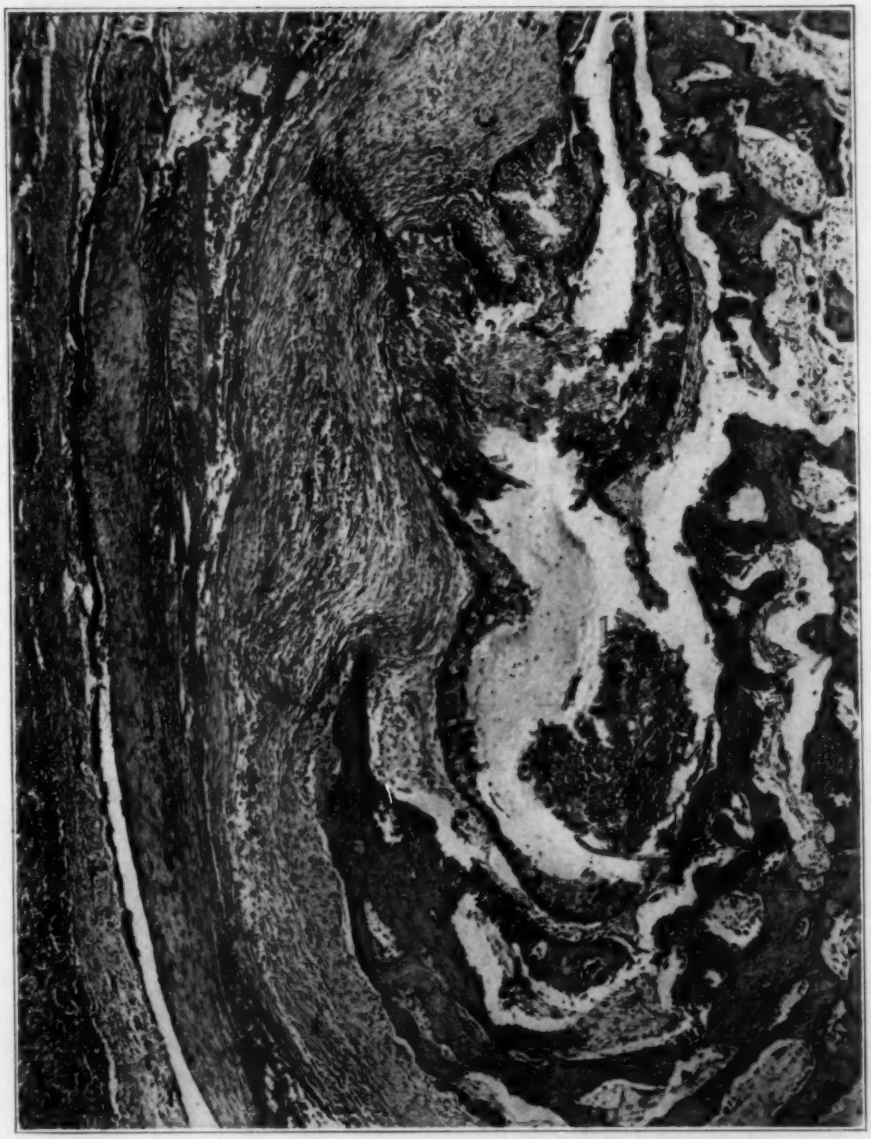

Fig. 6.—Section (× 140) of vesical epithelium and sheath of the rectus abdominis muscle transplanted to the spleen, at forty-seven days, showing formation of bone strictly confined to the transplant.

A similar change of tooth cell to osteoblast type is predicated in the present experiment, in which the tooth was transplanted from its normal environment to the abdominal wall.

EXPERIMENT 3.—*Transplantation of the epithelium of the urinary bladder to the abdominal fascia in the rat and guinea-pig, resulting in osteogenesis.*

Method.—In four rats and three guinea-pigs under ether anesthesia, the peritoneal cavity was opened, the urinary bladder exposed and the dome amputated.

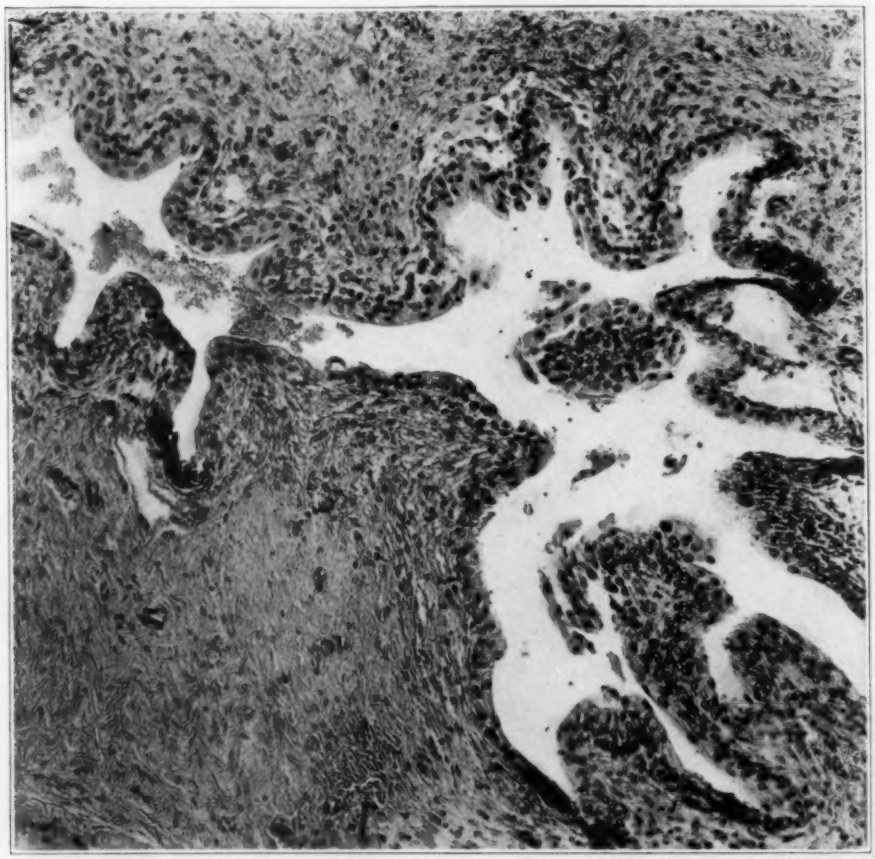

Fig. 7.—Section (× 140) showing vesical epithelium alone transplanted to the spleen at forty-seven days there is absence of bone formation, although the epithelium is surrounded by fibroblasts.

The excised epithelium was then sutured on the external oblique muscle. Closure of the bladder was effected with a purse-string suture of fine silk placed in the layers of muscle, infolding the cut surface.

Results.—In each case the transplant survived and formed a cyst, which was partly surrounded by a plaque of bone. The results correspond in every way with the findings in a similar experiment on the dog.[23b]

EXPERIMENT 4.—*Transplantation of mucosa of the urinary bladder to the spleen.*

Method.—In sixteen dogs, a large area of the mucosa of the bladder was isolated as previously described and the bladder closed. The strip of mucosa was then treated variously: (1) transplanted to the interior of the spleen; (2) sutured to a piece of connective tissue of similar size from the sheath of the rectus abdominis muscle, both tissues being transplanted together to the spleen, or (3) sutured on the surface of the spleen. Autopsy was performed between fifty and seventy-two days after the operation. Serial histologic sections were made of the transplant.

Results.—As previously reported,[23b] it was found that when mucosa of the bladder alone was transplanted to the spleen it survived and became surrounded by connective tissue but no ossification resulted, although when mucosa of the bladder was transplanted to the spleen with a connective tissue susceptible of ossification, such as the sheath of the rectus abdominis muscle (fig. 6), bone invariably formed.[44] However, when mucosa of the bladder was transplanted on the surface of the spleen, tiny spicules and traces of bone were found in four of six cases, the changes being observed by the use of serial sections.

EXPERIMENT 5.—*Transplantation of mucosa of the urinary bladder to the peritoneum.*

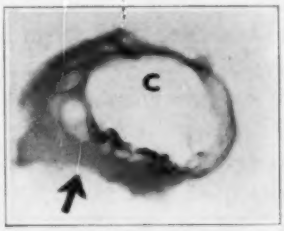

Fig. 8.—Roentgenogram of a specimen in an experiment in which vesical mucosa was transplanted to the external posterior surface of the same bladder for forty-nine days. The cyst (*C*) which formed with bone in the outer coat of the bladder may be seen. The arrow points to the mucosa of the bladder lumen.

Methods.—In nineteen dogs under ether anesthesia, large segments of mucosa of the bladder were elevated in the manner described and transplanted to various parts of the peritoneal cavity: (1) to the omental apron, which was then rolled up and sutured so that the transplant did not come in contact with the parietal peritoneum; (2) to the posterior surface of the urinary bladder, and (3) to the parietal peritoneum. Autopsy was performed from forty-nine to eighty-four days after the operation.

Results.—In every case bone was found. In the omentum, the bladder mucosa proliferated and formed a cyst partly surrounded by a plaque of bone immediately beneath the epithelium. On the outside of the bladder, similarly, a cyst was found with bone in the subperitoneal coat of the bladder (fig. 8). Likewise, in transplants to the parietal peritoneum bone was observed adjacent to the cyst in the connective tissue. The experiment was modified by fixing the epithelial patch in place with four long threads of silk anchored to the patch and entering the peritoneum 4 or 5 cm. from the patch, where they penetrated the abdominal wall; by

44. Huggins, C. B.: Proc. Inst. Med. Chicago **9**:89, 1932.

this technic there was no wound of the peritoneum closer to the patch than these needle holes. Typical bone formed, and a curious effect was achieved: Mucosa and connective tissue were seen growing along the threads as well as becoming locally adherent; the bone formation recovered consisted of a solid plaque the shape of the original patch, with four bony processes corresponding to the threads.

COMMENT

Experiments 1 and 2 show clearly that a local calcium depot is not a rapid stimulus for the formation of bone. To be reconciled with the experimental data, however, is the fact that frequently bone occurs in old calcified lesions. The explanation of this phenomenon may be found possibly in the fact that a longer period is necessary for apatite calcification to effect ossification than occurred in the present experiments, and hence that apatite salts may serve as a slow indolent stimulus to ossification. A separate explanation that may be provided is that the bone observed in pathologic conditions developed at the time of the original calcification and survived.

The experiments in which bone was formed as a result of the epithelial stimulus show that the same mechanism is at work in the guinea-pig and rat as in the dog; the epithelium that lines the urinary bladder of these animals is an osteogenic membrane. Ossification is prevented by a functional difference between connective tissues. It is interesting that the outer fibroblasts of the subperitoneal coat of the urinary bladder are not capable of resisting the bone-forming stimulus of the epithelium of the bladder, while the fibroblasts in the interior of the bladder must invariably resist it; the formation of bone in the urinary bladder has not been described, except in the Neuhof patches.[45]

SUMMARY

1. Transplantation of bone, hydrolyzed in strong alkali to destroy the organic elements, to the abdominal muscles and to replace defects in the skull and ribs did not stimulate the formation of new bone.

2. Transplantation of deciduous teeth to the abdominal muscles led to the formation of bone in these teeth. Boiling completely inhibited the formation of bone.

3. Epithelium of the urinary bladder transplanted to the abdominal wall in the rat and the guinea-pig led to formation of cysts and production of bone.

4. In the dog, epithelium of the urinary bladder transplanted into the spleen did not lead to formation of bone unless connective tissue capable of ossification was transplanted with it. Transplantation to the surface of the spleen led to the formation of a small amount of new bone in several cases.

45. Neuhof, H.: Surg., Gynec. & Obst. **24**:383, 1917.

5. The peritoneum and adjacent fibroblasts, including the omentum, easily ossified under the epithelial stimulus. This led to the conclusion that the subperitoneal fibroblasts in the outer coat of the bladder differ from the fibroblasts adjacent to the lining epithelium of this structure in that the former ossify when in contact with bladder epithelium while the latter do not. The defense against the ossifying action of the epithelium of the urinary bladder thus is topographically confined to the inside of the bladder and is lacking in the outside coverings of this viscus.

RELATION OF PATHOLOGIC CHANGES OF THE INTERVERTEBRAL DISKS TO PAIN IN THE LOWER PART OF THE BACK

DAVID SASHIN, M.D.
NEW YORK

My purpose in this presentation is to direct attention to a consideration of the importance of pathologic changes of the intervertebral disks, particularly those of the lower lumbar portion of the spine and of the lumbosacral junction, in the causation of pain in the lower part of the back. The intervertebral disks have until recently escaped careful investigation. Although the literature is full of papers on pain in the lower part of the back, they are, on the whole, concerned with the presentation of new theories, diagnostic procedures and methods of treatment. Few investigators have attempted to study the underlying pathologic condition. Schmorl [1] was the first to undertake a careful and comprehensive study of the intervertebral disks at autopsy. His contributions have greatly increased the knowledge of the anatomy and pathology of the disks.

ANATOMY

The normal adult intervertebral disk consists of a circumferential fibrous ring, called the annulus fibrosus, a highly expansile nucleus pulposus and two thin plates of hyaline cartilage. In the living state the nucleus is compressed by the contiguous plates of cartilage and the vertebral bodies and is prevented from expanding laterally by the annulus fibrosus. The annulus fibrosus consists of firm fibrous strands circumferentially arranged around the periphery of the body and surrounding the nucleus pulposus. The nucleus pulposus and the annulus fibrosus comprise the main substance of the intervertebral disks and are separated from the vertebral bodies by the two thin plates of hyaline cartilage (fig. 1).

Read before the Orthopedic Section, New York Academy of Medicine, May 17, 1935.

From the Orthopedic Service of Dr. H. Finkelstein, Hospital for Joint Diseases.

1. Schmorl, G.: Ueber die an den Wirbelbandscheiben vorkommenden Ausdehnungs- und Zerreissungsvorgänge und die dadurch an ihnen und der Wirbelspongiosa hervorgerufenen Veränderungen, Verhandl. d. deutsch. path. Gesellsch. **22**:250, 1927; Ueber Knorpelknötchen an den Wirbelbandscheiben, Fortschr. a. d. Geb. d. Röntgenstrahlen **38**:265, 1928; Ueber die pathologische Anatomie der Wirbelbandscheiben, Beitr. z. klin. Chir. **151**:360, 1931.

The disks form one quarter of the total length of the spine. They vary in size, being widest and thickest in the lumbar region and smallest in the dorsal region. In the lumbar region they form a third of its length.

The normal adult intervertebral disks have no blood vessels. They receive nourishment from the bone marrow of the bodies by diffusion.

The disks permit a considerable range of motion of the spine. Owing to the expansibility and turgor of the nucleus pulposus, the disks impart great flexibility to the spine. They act as a buffer or shock absorber for the strain and stress of daily activity. Mobility of the spine is greatest in the cervical and lumbar regions and least in the dorsal. Flexion is freest and most extensive in the lower lumbar portion of the spine. Goldthwait,[2] in 1910, determined that one half of the motion of the trunk below the lower dorsal region is made up of motion in

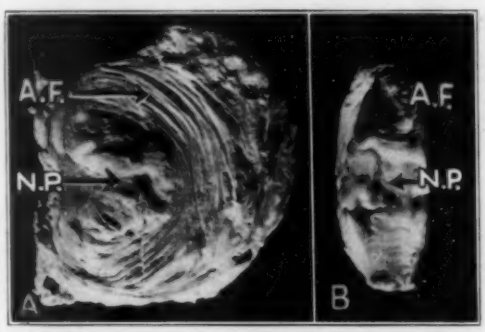

Fig. 1.— *A*, an intervertebral disk of the lumbar portion of the spine of an adult. Note the bulging nucleus pulposus (*N.P.*) surrounded by the circumferential fibrous ring, the annulus fibrosus (*A.F.*). *B*, cross-section of an adult lumbar intervertebral disk, showing the nucleus pulposus (*N.P.*) and the annulus fibrosus (*A.F.*).

the lumbosacral intervertebral disk and in the joint above it. The remainder of the motion is distributed between the rest of the lumbar portion of the spine and the sacro-iliac joints.

PATHOLOGY

Pathologic changes of the intervertebral disks are frequently noted at autopsy. They may be found after the first decade of life but are mainly seen after the third and increase in frequency with age. The changes vary from a small herniation from the disk into the vertebral

2. Goldthwait, J. E.: The Lumbo-Sacral Articulation: An Explanation of Many Cases of "Lumbago," "Sciatica" and Paraplegia, Boston M. & S. J. **164:** 365 (March 9) 1911.

bodies to beginning vascular infiltration of the substance of the disk, fibrous replacement of nuclear tissue, brown degeneration, calcification of the nucleus, and, in late stages, shrinkage, narrowing and ossification of the disk (figs. 2 and 3). In a sagittal section of an adult spine one or more of these changes may be noted in the disks. Because of the lack of mobility of the dorsal portion of the spine, these changes take place early and gradually lead to complete absence of motion.

In the lumbar region, because of the size, strength and increased mobility of the disks, the pathologic changes of the disk substance have

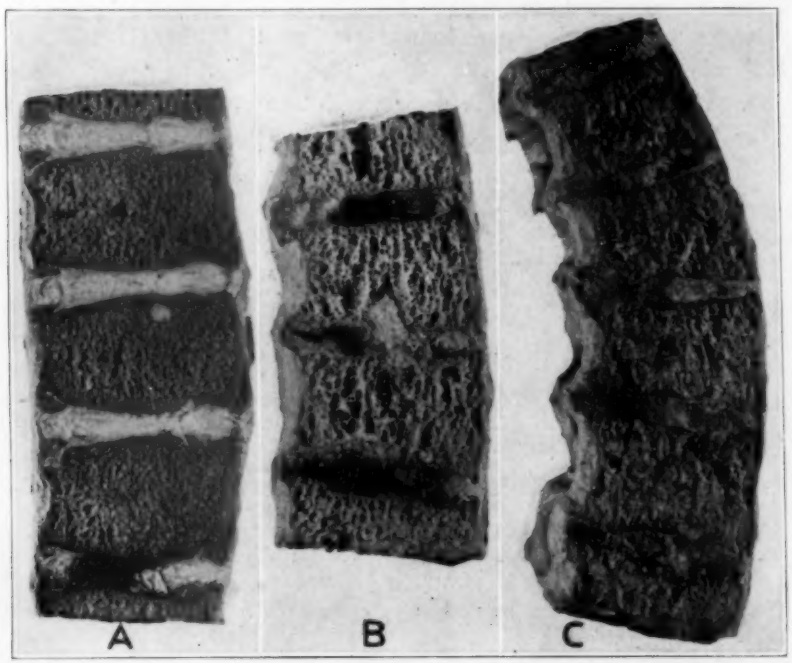

Fig. 2.—In *A* may be seen discoloration and beginning degeneration of the lowest disk; *B* shows advanced degenerative changes, with herniations and narrowing of the disks, and *C*, degenerative changes, with ossification of the disks anteriorly.

a pronounced effect on the functional activity and resistance of the spine. When degenerative changes are present in the lower lumbar and lumbosacral intervertebral disks, the flexibility and mobility of the spine are considerably diminished, and its capacity to withstand the strain and shocks of functional activity is greatly reduced.

When a sagittal section of the spine is examined post mortem, one frequently finds herniation from the disks into the adjacent bodies. These invasions are usually of small size but often may extend for a

considerable distance into the substantia spongiosa. Schmorl,[1] in an examination of three thousand spines, found herniation from the disks in 38 per cent of them.

The great majority of the herniations from the disks are not visualized by roentgen rays. They are seen only when a sclerosing layer of bone surrounds the disk or when there is a break in the cortical plate of the vertebral body. Their importance lies in the fact that, with the

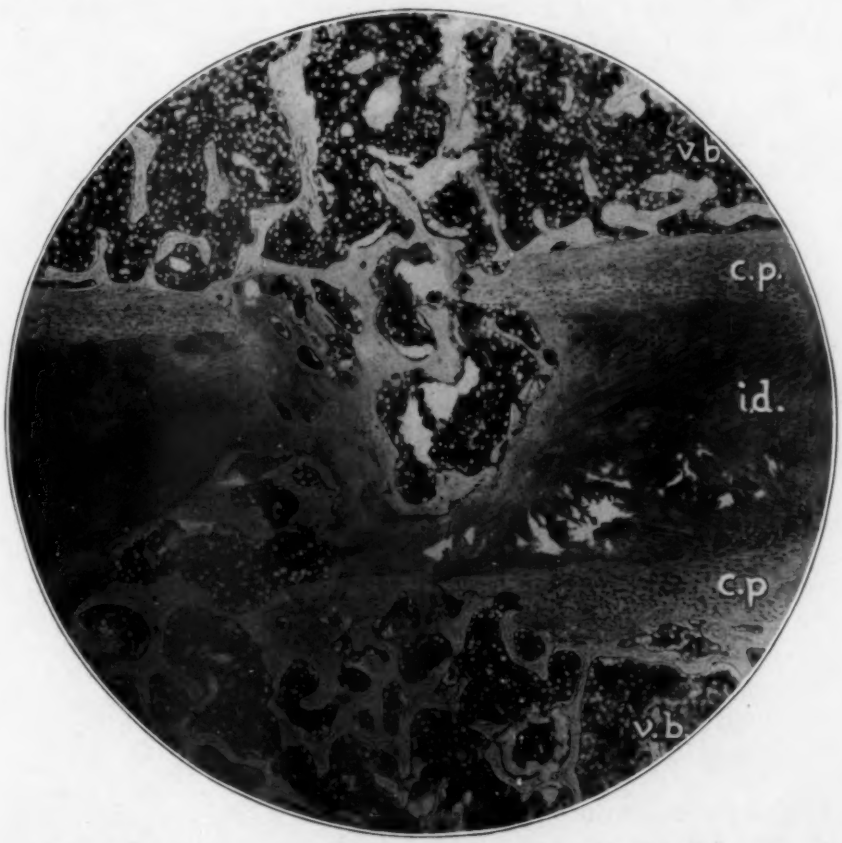

Fig. 3.—Low power photomicrograph of an intervertebral disk (*i.d.*) and adjacent vertebral bodies (*v.b.*), showing vascular infiltration and ossification of the disk. Note the break through the upper and lower cartilage plates (*c.p.*).

formation of a herniation from the disk, an avenue is produced for the extension of blood vessels from the substantia spongiosa into the substance of the disk proper. With vascular infiltration, the highly expansile gelatinous matrix of the nucleus pulposus is replaced by fibrous tissue. Gradual fibrillar degeneration with loss of fluid of the nucleus pulposus sets in, resulting in the disk's shrinking and becoming firm.

Another consequence of a prolapse of the disk is that in large herniations a considerable portion of the matrix of the nucleus pulposus may extend into the body, resulting in shrinkage and narrowing of the disk substance. With a reduction in its size, movements in the disk are restricted, and stiffness results. Püschel,[3] in a study of the water content of a series of normal and degenerated intervertebral disks, found that the water content of the disks is greatest at birth and decreases with age. The figures for the degenerated disks are markedly lower than those for the normal ones.

Marked degenerative changes of the substance of the disk are often seen without any evidence of the herniation of the disk into the vertebral bodies or of extension of the disk into the spinal canal. These

Fig. 4.—Section through the fourth lumbar and the lumbosacral intervertebral disk, showing marked degenerative changes and narrowing of the disks. Note the disk node in the fourth lumbar body.

changes result from the general wear and tear of daily activity. They are more commonly seen in the aged and in men doing hard, laborious work. The lumbosacral disk, because of the increased strain, mobility and weight-bearing function to which it is subject, is a frequent site of early degenerative changes, with resulting shrinkage and narrowing of the disk (fig. 4). With the onset of pathologic changes, the nucleus loses its normal elasticity and turgor, becoming firm, dense and immobile. The spine loses its flexibility, resilience and buffer function, and, as the process goes on, bony changes of the bodies become evident, with resulting stiffness of that part of the spine.

3. Püschel, J.: Der Wassergehalt normaler und degenerierter Zwischenwirbelscheiben, Beitr. z. path. Anat. u. z. allg. Path. **84**:123, 1930.

When a partly macerated spine of a young adult with the intervertebral disks intact is carefully studied, one observes that the articular surfaces of the posterior articular facets are in close contact with and parallel to each other when the column of lumbar bodies is in slight lordosis. When one attempts to flex forcibly the lumbar portion of the spine, a slight compression of the disk occurs anteriorly, and with it a slight separation and overriding of the articular facets take place. In like manner, when one of the lumbar disks is removed, the adjacent bodies tilt forward and separate posteriorly. At the lumbosacral area, because of the angulation, size and position of the disk with its base, or greatest thickness, in front and the narrowest in the back, the effect is more pronounced. Here, a narrowed disk produces a marked separation of the articular facets with resulting increase of the lumbosacral angle and flattening of the back. Thus, as the normal alinement of the lumbar vertebrae is changed, the normal physiologic relationship of the muscles and ligaments of the lower part of the back is disturbed. Muscle spasm and pain result. With a marked separation of the articular facets, such as occurs when the lumbosacral disk is involved, pathologic changes set in in the small joints, with stretching and distention of the joint capsule, often resulting in pressure on the fifth lumbar nerve root as it passes through the intervertebral foramen. Danforth and Wilson,[4] in a study of the lumbosacral region in relation to sciatic pain, found that the foramen between the fifth lumbar vertebra and the sacrum is always the smallest and the one between the fourth and the fifth lumbar vertebra the next larger. In contrast to the size of the foramen, the fifth lumbar nerve root is the largest and the fourth lumbar nerve root is next largest. Thus, when one considers that the fourth and fifth lumbar nerve roots are important parts of the lumbosacral plexus and that the largest nerve root passes through the smallest canal, the possibility of impingement of the nerve with resulting radiating pain down the limb becomes apparent.

ETIOLOGY

Degenerative changes of the disks are due mainly to the wear and tear of daily functional activity. The process is gradual and increases with age. When functional activity is moderate, the disk undergoes only slight changes, and the spine may maintain its flexibility and mobility throughout life. When daily functional activity entails heavy physical labor, marked degenerative changes of the disk develop. The disk becomes dry and firm, loses its flexibility and becomes less adaptable and less resistant to the strain and stress of daily activity. This process

4. Danforth, M. S., and Wilson, P. D.: The Anatomy of the Lumbo-Sacral Region in Relation to Sciatic Pain, J. Bone & Joint Surg. **7**:109 (Jan.) 1925.

may go on without any noticeable evidence of physical impairment or subjective complaints until a slight trauma, such as lifting a heavy object, a sudden twist or a misstep, precipitates a train of symptoms and physical signs that completely incapacitate the person. The trauma, although slight, is often sufficient to produce a compression of a pathologic disk.

A severe, sudden injury to the spine is an etiologic factor of far less frequency. An evidence of sudden, severe trauma is the finding of breaks in the cartilage plates and small fresh hemorrhages around the herniations from the disk (fig. 5). The effect of the trauma depends not so much on the intensity of the traumatic agent as on the condition of the disk and its capacity to withstand it. With the exception of severe injuries that result in a fracture of the bone, an injury, such as a heavy blow or fall, which in a young person may give rise only

Fig. 5.—Low power photomicrograph of an extension of an intervertebral disk (*I.D.E.*) into the proximal vertebral body. Note the marked vascular infiltration and dilatation of the vessels surrounding the disk node.

to slight discomfort, will result in pain and lengthy disability in an older person. The difference in resistance and adaptability is due in a large measure to the condition of the intervertebral disks. Thus, in the young, the disks are expansile and possess a great capacity to absorb and "cushion" shocks and stresses, while in persons in late adult life, the disks are firm, their resilience is reduced and the cushion or buffer capacity is greatly diminished.

CLINICAL PICTURE

The clinical picture of the pathologic disks is not clearly demonstrable. There are no distinct signs or symptoms especially characteristic of this condition. The changes that occur are usually not isolated but are rather the result of the general process of wear and tear affecting the spine and other parts of the body. Arthritic changes of the

articular facets and osteophytes around the margins of the bodies are usually associated and often result from a disturbance in the normal function of the disks. Subjective complaints and disabilities which these patients have are essentially an indication of a compromised and weakened spine.

In my series of cases of narrowed disks the main symptoms complained of were dull aching pains in the lower part of the back. Many of the patients had pain radiating down the backs of the lower limbs along the course of the sciatic nerve. The history of onset frequently given was of a slight injury, such as a slight fall, a sudden twist or the lifting of an object. Few were unable to recall any injury.

On examination, the patients walked guardedly. The lower lumbar portion of the spine was held rigid and was often tilted to one side. Motion of the spine was restricted. Tenderness was present over the lumbosacral junction. There was often tenderness over the gluteal region, the area supplied by the superior gluteal nerve. Straight raising of the leg was limited when associated sciatic pain was present. Hyperextension of the spine gave rise to pain when the lumbosacral disk was involved.

ROENTGENOLOGIC OBSERVATIONS

Roentgenograms of the spine, particularly lateral and oblique views, established the diagnosis of narrowing of the disk. The intervertebral space was narrowed, and the lumbar portion of the spine was flattened. With the involvement of the lumbosacral disk, the lumbosacral angle was increased, and often a separation of the articular facets could be seen on the oblique views. Degenerative changes of the disks when associated with herniation of the disk into the vertebral bodies could be noted on the roentgenogram as small areas of lessened density surrounded by a sclerotic layer of bone. Calcifications of the nucleus pulposus were distinctly visualized.

TREATMENT

The treatment consisted in an attempt to reestablish the normal lumbar lordosis and to support the spine by means of a plaster of paris jacket. My aim was to realine the spinal structure to the normal or as near to the normal as possible, and thus to relax the muscles and ligaments of the back. This might be accomplished by placing the patient on a convex frame or a padded plaster of paris bed for several weeks followed by an application of a plaster of paris jacket. I have obtained the best results by gently hyperextending the spine, while the patient was under general anesthesia, until the normal lumbar lordosis was reached. A plaster of paris jacket was then applied from the upper part of the chest to the pelvis, holding the spine in the corrected position.

No forcible manipulation was used. In cases in which the spine was rigid and a fixed deformity was present, I did not attempt to correct it forcibly, but rather tried to obtain the best hyperextension position possible and to support the spine by means of a plaster of paris jacket or spica cast extending from the chest down to the toes of the involved leg.

REPORT OF CASES

CASE 1.—H. S., a white man aged 46, was admitted to the hospital with a complaint of pain over the lower part of the back and of radiating pain down the left leg. The condition came on suddenly four months before admission, while he was working.

Fig. 6 (case 1).—Oblique view, showing the narrowed lumbosacral intervertebral space with an increased lumbosacral angle.

Examination.—The patient was well developed and well nourished. He walked guardedly, with his body tilted to the left. His spine was held rigid. Motion was restricted in all directions. There was tenderness over the lumbosacral junction and over the left sacro-iliac area. A straight leg-raising test gave negative results. The double thigh flexion test gave positive results. Hyperextension of the spine gave rise to pain over the lumbosacral region.

Anteroposterior, lateral and oblique roentgenograms revealed a narrowed lumbosacral intervertebral space, with an increase of the lumbosacral angle (fig. 6).

Treatment.—Under general anesthesia the lumbar portion of the spine was gradually hyperextended, reestablishing the normal lumbar lordosis. A plaster of

paris jacket extending from the upper ribs to the pelvis was then applied, holding the lumbar portion of the spine in lordosis.

CASE 2.—N. H., a white man aged 46, was admitted to the hospital with a complaint of radiating pain down the backs of both legs and pain over the lower part of the back. He gave a history of having many similar attacks since 1917, each of which lasted several weeeks.

Examination.—The patient was well developed. He walked guardedly, holding to objects for support. His body was tilted to the left. The spine was held rigid and flat. The lumbar curve was obliterated. Motion was restricted in all directions. There was spasm of the lumbar muscles. The straight leg-raising

Fig. 7 (case 2).—Lateral view, showing the narrowed fourth lumbar intervertebral space (marked by the arrow), with obliteration of the normal lumbar lordosis.

test gave positive results on both sides. The double thigh flexion test gave negative results.

Anteroposterior, lateral and oblique roentgenograms revealed a distinct flattening of the intervertebral disk between the fourth and the fifth lumbar vertebra and slight anterior luxation of the fifth lumbar vertebra (fig. 7).

Treatment.—Under general anesthesia the lumbar portion of the spine was gradually hyperextended, reestablishing the normal lumbar lordosis. A plaster of paris jacket extending from the upper ribs to the pelvis was then applied, holding the lumbar portion of the spine in lordosis.

CASE 3.—Y. L., a white woman aged 35, came to the clinic with a complaint of pain over the left buttock and the lower part of the spine, with radiating pain

down the back of the left limb. The condition came on insidiously eight months before admission.

Examination.—The patient walked with a slight limp and with the spine tilted to the left. There was a slight left lumbar (sciatic) scoliosis. Motion of the spine was considerably restricted in all directions. There was tenderness over the right sacro-iliac region and the right gluteal region.

Roentgenograms revealed pronounced narrowing of the intervertebral disk between the fourth and the fifth lumbar body. The normal lumbar lordosis was obliterated (fig. 8).

Fig. 8 (case 3).—Pronounced narrowing of the fourth lumbar intervertebral space, with reversal of the normal lordosis to a slight kyphosis.

Treatment.—Traction was applied on a convex frame for several weeks. Later the spine was hyperextended, and a plaster of paris corset was applied, holding the lumbar spine in slight lordosis.

CASE 4.—M. M., a white man aged 50, came to the clinic complaining of pain over the lower part of the back and of shooting pains and numbness down the back of the left leg. The condition came on after a game of hand ball several months before admission.

Examination.—The patient was obese and well developed. His spine was held rigid, with the body tilted to the right. He was unable to bear any weight on

the left leg. Left lumbar (sciatic) scoliosis was present. The lumbar portion of the spine was flat. Motion was restricted in all directions. A straight leg-raising test gave positive results on the left side. The double thigh flexion test gave negative results. Hyperextension of the spine gave rise to pain over the lumbosacral region.

Roentgenograms revealed that the fifth lumbosacral intervertebral space was narrowed and that the lumbar portion of the spine was flat. The lumbosacral angle was slightly increased.

Fig. 9 (case 5).—A narrowed intervertebral disk (*i.d.*) between the second and the third lumbar vertebra (*l.v.*). Note the semicircular area of lessened density indicative of a disk herniation at the upper margin and posterior third of the third lumbar vertebra (*3 l.v.*).

Treatment.—The spine was hyperextended, and a plaster of paris jacket was applied, holding the lumbar portion of the spine in slight lordosis.

CASE 5.—J. Z., a white man aged 32, was admitted to the hospital with the chief complaint of pain over the lower part of the back of several years' duration.

Examination.—The patient was well developed and walked with a limp to the right. The dorsolumbar portion of the spine was held rigid. Tenderness was present over the second lumbar vertebra. The straight leg-raising test gave positive results.

Roentgenograms revealed a narrowed intervertebral disk between the second and the third lumbar vertebra, with evidence of herniation from the disk into the third lumbar body (fig. 9). The normal lumbar lordosis was obliterated.

Treatment.—A plaster of paris jacket was applied.

CASE 6.—E. J., a white man aged 26, complained of pain in the lower part of the back. He gave a history of falling eight months before admission.

Examination.—The lower part of the back was rigid. Motion of the spine was considerably restricted. Spasm of the sacrospinalis muscles was present. The double thigh flexion test gave positive results. Hyperextension of the spine gave rise to pain in the lumbosacral junction.

Roentgenograms revealed a narrowed lumbosacral intervertebral space.

Treatment.—The spine was hyperextended, and a plaster of paris jacket was applied, holding the spine in slight lordosis.

CASE 8.—S. V., a white woman aged 59, came to the clinic with a complaint of pain over the lower part of the back and of shooting pain down the back of both limbs. Pain was constant. The duration was four weeks and the onset was insidious.

Examination.—The body was tilted to the left. Lumbar lordosis was considerably diminished despite the presence of a prominent abdomen. There was tenderness over the lumbosacral junction. Motion of the spine was not restricted.

Roentgenograms revealed osteoporosis of the spine and a marked compression and narrowing of the lumbosacral intervertebral disk, with sclerosis of the bony surfaces.

SUMMARY

Pathologic changes of the intervertebral disks are commonly observed at autopsy. The changes that take place vary from small herniations of the disk through vascular infiltration of the disk substance, fibrous replacement of the elastic tissue, brown degeneration, and finally shrinkage, narrowing and calcification of the entire disk. As a result, the disks lose their flexibility and resilience. They become firm, immobile and less resistant to the stress and shock of functional activity.

When a disk is narrowed anteriorly, the normal lumbar lordosis is diminished, and the articular facets are slightly separated. When the lumbosacral disk is narrowed, the lumbosacral angle is increased, and there results a considerable separation of the articular facets. As a result of the malalinement of the facets arthritic changes take place, with consequent muscle spasm, pain and often impingement of the fifth lumbar nerve root resulting in sciatic pain down the leg.

Clinically the diagnosis of a narrowed intervertebral space is made from the roentgenograms, especially from the lateral and oblique views.

Seven cases in which there was roentgenographic evidence of a narrowed intervertebral space are reported, and the clinical course is reviewed. Pain in the lower part of the back was a constant complaint. In some cases there was associated sciatic pain down the leg. The treatment consisted in reestablishing the normal lumbar lordosis under general anesthesia and supporting the spine by means of a plaster of paris jacket.

ALTERATIONS IN THE VISUAL FIELDS FOLLOWING CRANIOCEREBRAL INJURIES

CARL WHEELER RAND, M.D.
LOS ANGELES

During the past decade injuries to the brain have been analyzed in greater detail than ever before. The recognition of localizing signs and symptoms consequent to these injuries, from the standpoint both of prognosis and of treatment, is of great importance. For example, in a group of cases of injury to the head the cranial nerves may be studied collectively, or one's attention may be profitably limited to the study of a single nerve and its intracranial ramifications. The following observations are confined to injuries of the optic nerves and their pathways, as revealed by alterations in the visual fields.

Loss of vision, a serious complication following head injuries, fortunately is not frequent. Phelps [1] found injury to the optic nerves six times in two hundred and forty-five cases of fractures of the base of the skull (2.4 per cent). This relative infrequency is surprising when one considers the extensive ramifications of the entire visual mechanism and bears in mind the great variety of methods by which craniocerebral injuries are produced. Somberg [2] pointed out that a patient may overlook moderate visual defects because of the overlapping of the binocular fields. While the types of visual defects following injury to the visual pathways are many, they may be accurately outlined. In discussing them it is necessary to consider traumatic lesions occurring along the visual pathways, from the retinas to the tips of the occipital lobes (fig. 1). Organic lesions tend to leave permanent visual defects. Changes in the fields due to hysteria, on the other hand, being functional, are usually less permanent. The latter, however, probably constitute the larger group. In such cases, for fear of "fixing" the neurosis, it is unwise to place undue emphasis on the visual defect by repeated examinations. In this presentation alterations in the fields resulting from organic, rather than from functional, conditions will be given primary consideration.

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1. Phelps, Charles: Traumatic Injuries of the Brain and Its Membranes, New York, D. Appleton & Company, 1897, p. 25.

2. Somberg, J. S.: Traumatic Lesions of the Optic Pathways with Report of a Case, Am. J. Ophth. **10**:115 (Feb.) 1927.

INJURIES TO THE RETINAS AND OPTIC NERVES

As the eye constitutes an integral part of the central nervous system, injury to this organ must be given consideration. Retinal and preretinal hemorrhages, edema about the macula, commotio retinae and detachment of the retina should be mentioned. Such conditions may follow direct injury to the eyeball or occur secondarily as a result of trauma to the head. Hippocrates realized that amaurosis sometimes followed wounds inflicted on the eyebrows or calvarium. Retinal hemorrhages of various sorts may give rise to corresponding scotomas. Detachment of the retina is followed by varying forms of defects in the field. The visual disturbances secondary to commotio retinae or hemorrhage tend to clear

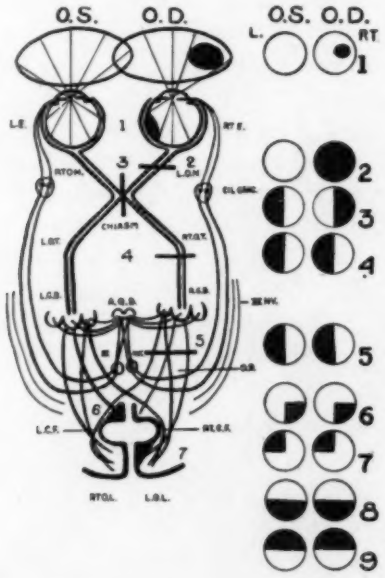

Fig. 1.—Diagrammatic representation of the visual pathways, with characteristic types of defects in the peripheral visual fields (after Gill[3]): (1) lesion of the retina in the nasal portion of the right eye with scotoma in the temporal field of the right eye; (2) lesion of the right optic nerve with complete loss of vision in the right eye; (3) lesion involving the optic chiasm, producing bitemporal hemianopia; (4) lesion involving the right optic tract with left homonymous hemianopia; (5) lesion involving the right optic radiations producing the same type of defect as that observed in (4); (6) lesion involving the anterior portion of the left calcarine fissure producing an inferior homonymous quadrantic anopsia; (7) lesion involving the posterior portion of the right calcarine fissure, producing a left superior homonymous quadrantanopia; (8) a combination lesion involving the anterior portion of both right and left calcarine fissures producing a bilateral inferior altitudinal hemianopia; (9) lesion of both posterior portions of the calcarine fissures, producing a bilateral inferior altitudinal hemianopia.

up; those consequent to detachment of the retina are permanent unless they are surgically corrected.

Rarely, a transient choking of the disks, for which no plausible explanation is at hand, may follow a head injury. During its presence one finds lowering of the acuity of vision, general contraction of the visual fields and enlargement of the blindspots such as occur in cases of papilledema secondary to tumor of the brain. The fields improve as the choking subsides. Most frequently choking of the disks accompanies chronic subdural hematoma, abscess of the brain or pneumocephalus. If the lesion brings pressure to bear on the visual pathways, defects in the fields occur, and they become permanent unless the cause is removed.

Gill [3] stated that loss of vision following hemorrhage into the orbit is slowly, rather than suddenly, progressive. Hemorrhage under the sheath of an optic nerve, frequently associated with fracture of the orbit, impairs or destroys vision. As this sheath is a prolongation of the dura, subdural or subarachnoid hemorrhages may find their way beneath it (fig. 2, Cohen [4]), causing pressure on the visual fibers (fig. 3, Liebrecht [5]). Again, rupture of the central artery or vein (fig. 4) or acute angulation at their point of emergence from the nerve is said to cause blindness.

Commonly, injury to the optic nerves follows a gunshot wound of the head. One frequently finds a person blinded in one or in both eyes as a result of having the optic nerves severed by a bullet. Orbital fractures, especially those involving the optic foramen, cause monocular, rarely binocular, blindness. Miceli [6] reported the instance of a patient with a fracture involving the right optic canal who subsequently died of pneumonia. Postmortem examination showed the optic nerve to be thickened in a clublike manner, the greater swelling being toward the anterior extremity. Microscopically the intervaginal space was increased, the increase being more marked distally. The nerve fibers in the lamina cribrosa were tightly packed, small vacuoles of varying size being interposed between the tracts. Ovoid lacunae, some of which penetrated the distal sheath, were present on the arachnoid side.

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3. Gill, W. D.: Eye Symptoms in Head Injuries, M. Rec. & Ann. **25**:675 (Feb.) 1931.

4. Cohen, Martin: The Value of Eye Manifestations Complicating Fractured Skull: Preliminary Report, Arch. Ophth. **46**:258 (May) 1917.

5. Liebrecht: Schädelbruch und Auge, Arch. f. Augenh. (J. F. Bergman, Munich) **55**:36, 1906; Schädelbruch und Sehnerv, Arch. f. Ophth. **83**:525, 1912.

6. Miceli, I.: Alterations in Optic Nerve Following Injuries to Head, Gior. di ocul. **6**:45, 1925.

Smith [7] stated that von Holder found the walls of the orbit fractured seventy-three times in a series of eighty-six cases of fracture of the base of the skull. In the majority of cases the orbital fracture affected both the optic foramen and the optic canal. Under such circumstances one would expect that the optic nerve would be injured. Unless special attention is paid to this region, an orbital fracture is easily overlooked at postmortem examination. Such a fracture is frequently difficult to demonstrate in roentgen examination.

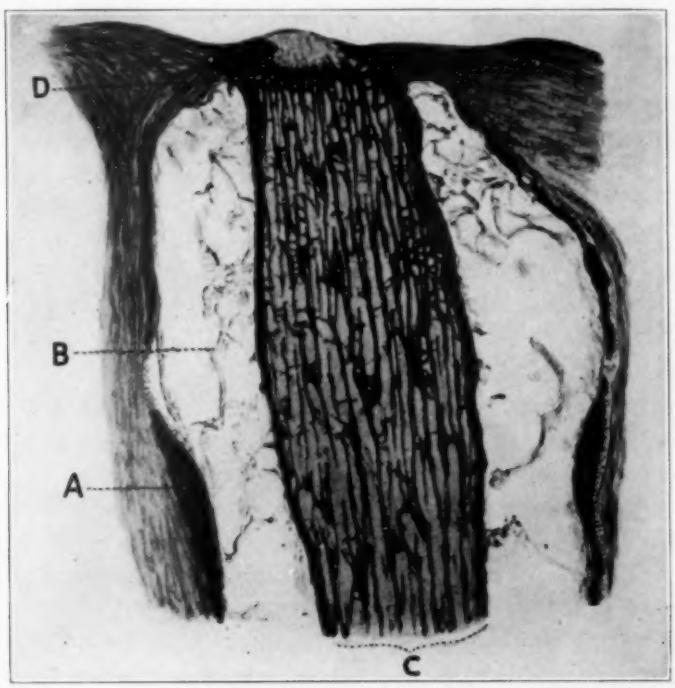

Fig. 2.—Drawing of microscopic section, showing: *A*, a subdural hemorrhage in the intervaginal space; *B*, a distended subarachnoid space devoid of hemorrhage; *C*, marked compression of the optic nerve fibers, and *D*, moderate upward displacement of the lamina cribrosa. (After Cohen.[4])

Callan [8] reported four cases of orbital traumatism with immediate monocular blindness. He collected from the literature reports of eighty

7. Smith, A. E.: Impairment of Vision Following Head Injury, Minnesota Med. **14**:809, (Sept.) 1931.

8. Callan, P. A.: Four Cases of Orbital Traumatism Resulting in Immediate Monocular Blindness Through Fracture into the Foramen Opticum, J. A. M. A. **18**:284 (March 5) 1892.

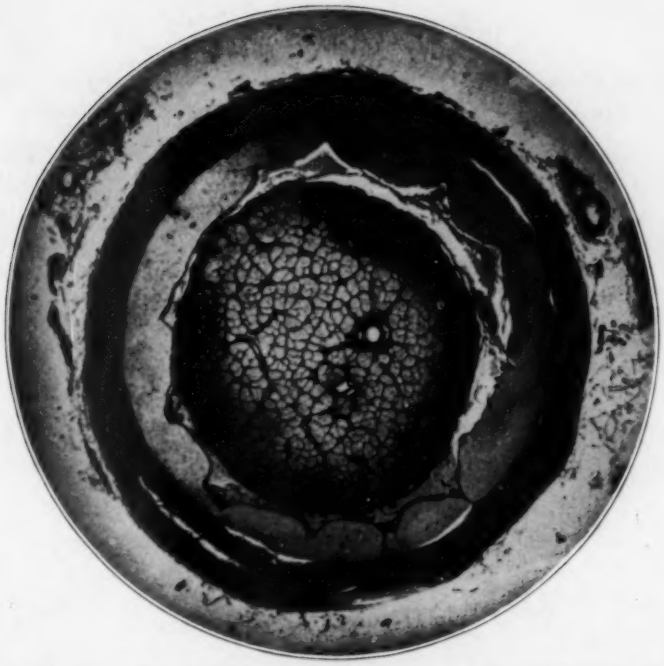

Fig. 3.—Cross-section of an optic nerve particularly showing bleeding into the subdural space. The subarachnoid space is dilated by lymph and some bleeding. (After Liebrecht.[5])

Fig. 4.—Diagrammatic representation of an optic nerve showing bleeding from the central vein. The vaginal space is widely dilated by lymph and blood. Detachment of the retina was present. (After Liebrecht.[5])

cases of fracture into the optic foramen. He explained the mechanism of the fracture as follows:

> The frontal bone unites with the nasal, submaxillary, lachrymal, and ethmoid bones by a continuous line of sutures, until the lesser wing of the sphenoid is reached, and at this point, the suture line bifurcates forming an obtuse angle, and quite near the apex of the angle is the foramen opticum. The jar made by the blow would find its weak point along this line of sutures, and the first resistance would be at the bifurcation adjacent to the foramen opticum. The movement or jar could not follow both lines with equal force at and beyond the bifurcation, consequently the unequal strain would result in fracture of the bone into the foramen opticum, causing compression of the optic nerve and sudden loss of vision in the eye.

Some writers have advocated decompression of the optic canal or exploration of the optic nerve in such cases of monocular blindness. The results of these attempts have been almost uniformly disappointing. Nothing can be expected if the nerve is crushed or severed; possibly better results may be obtained if it is infiltrated by blood or moderately compressed, as the sheath can be opened and pressure on the nerve relieved.

Plum [9] advised immediate operation when a fracture through the optic foramen results in monocular blindness.

Eagleton [10] stated: "Very slight pressure on the nerve itself as it passes through the bony optic foramen may cause loss of sight, which, if not early recognized and surgically relieved, will rapidly result in permanent blindness." I have not explored the optic nerve under these conditions. Perhaps such exploration should be recommended. While usually carrying little risk, such a procedure may occasionally be hazardous, as the following case indicates: A man aged 29 sustained multiple fractures of the left orbit, easily demonstrated roentgenologically. No fragments were displaced. Immediate ophthalmoplegia and monocular blindness resulted. Aside from these complications the patient apparently made an uneventful recovery. Two months later sudden fatal hemorrhage from the left nostril ensued. Autopsy revealed a healed fracture of the left orbital plate and frontal bone with recent erosion of the wall of the left cavernous sinus. At no time was a murmur present. The fatal hemorrhage might have occurred at operation.

INJURIES TO THE OPTIC CHIASM

From the standpoint of their mechanical production injuries to the optic chiasm are highly interesting. The mechanism of their production

9. Plum, F. A.: Ophthalmological Symptoms Associated with Intracranial Injuries, West. J. Surg. **39**:754 (Oct.) 1931.

10. Eagleton, W. P.: Traumatic and Infective Lesions of the Head, the Chief Manifestations of Which Are Visual Disturbances: Their Diagnosis and Surgical Treatment, S. Clin. North America **68**:1435 (Dec.) 1926.

has not been satisfactorily explained. As there is great variation in the relation of the chiasm to its surrounding structures, certain anatomic factors must be borne in mind. Walker,[11] in citing the work of Schaeffer, stated:

> . . . the chiasm was found to fit in close relationship with the chiasmal sulcus in only five per cent of the cases, while in four per cent the chiasm was located entirely behind the diaphragm, resting on the posterior sella. In twelve per cent the chiasm covered the central portion of the diaphragm, while in seventy-nine per cent the chiasm covered only the posterior half of the diaphragm, with the posterior part of the chiasm projecting variously over the dorsum sellae.

One must also bear in mind the wide variation existing in the size and shape of the sella turcica, with especial reference to variability in the prominence of the clinoid processes. Naffziger[12] mentioned an instance in which total blindness followed a fall from a hay wagon, resulting in dislocation of a long-standing pituitary tumor which had previously caused insignificant symptoms. He also cited an instance in which after a fracture of the anterior fossa and squamous portion of the right temporal bone monocular blindness developed on the third day. Death occurred two weeks later, resulting from pneumonia. Naffziger stated: "Autopsy revealed a displacement of the right anterior clinoid downward compressing the nerve to a flattened ribbon of about one third its normal thickness. In front of the compressed portion the nerve and its envelope were very bulbous and edematous."

When injured, the chiasm is frequently split in an anteroposterior direction, as represented by Liebrecht.[5] In his illustration, besides the sagittal tearing of the chiasm a transverse, almost complete, laceration of the left optic nerve is shown (fig. 5). Such lesions can be produced experimentally (fig. 6).

Recently Coppez[13] reported three cases of bitemporal hemianopia and panoramic scotoma. He attempted to explain the mechanism of these chiasmatic syndromes. He believed that the injury may occur in one of three ways:

1. As a result of a violent injury of the frontal region, which increases the transverse diameter of the skull. In discussing such lesions Coppez referred to the proposition of Liebrecht.[5] Félizet[14] had already shown that this diameter could be increased as much as

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11. Walker, C. B.: Lesions of the Chiasmal Region, Am. J. Ophth. **13**:198 (March) 1930.

12. Naffziger, H. C.: Certain Eye and Ear Affections in Association with Head Injuries, Ophth. Rec. **25**:502, (Oct.) 1916.

13. Coppez, Henri: Le mécanisme des lésions du chiasma dans les fractures du crâne, Arch. d'opht. (Masson & Cie, Paris) **46**:705 (Dec.) 1929.

14. Félizet, G. M.: Recherches anatomiques et expérimentales sur les fractures du crâne, Paris, A. Delahayer, 1873.

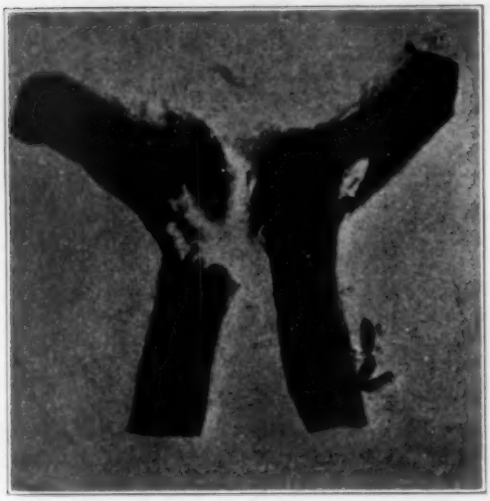

Fig. 5.—Longitudinal splitting of the chiasm with cross-tearing of one optic nerve following a fracture of the base of the skull. This type of lesion may be produced by traction on one optic nerve, causing total blindness in one eye and temporal hemianopia in the opposite visual field. (After Liebrecht.[5])

Fig. 6.—Anteroposterior separation of the commissure shown experimentally on the cadaver. When the glabella is widely spread the optic nerves separate, producing anteroposterior splitting of the chiasm. This is not tenable clinically. (After Coppez.[13])

8 mm. without actual fracture occurring. In order to cause fracture, greater violence is necessary. If sufficient force is used to fracture the ethmoid region in an anteroposterior direction, the distance between the optic canals will be increased and consequent spreading of the chiasm will occur. If the chiasm is completely split, bitemporal hemianopia will result. If some of the bundles of crossed fibers are spared, islands of vision will remain in the temporal fields. Coppez [13] reproduced these lesions experimentally on fresh cadavers. He stated that if the disjunction was increased until the nerve spread reached 26 mm., the anteroposterior rent of the chiasm was complete. He added that the nerves, being held tightly by the dural sheath, always remain in the optic canal. He admitted that it is difficult to believe that this could happen during life (fig. 6).

2. As a result of anterolateral fracture with destruction of the external walls of the orbit extending to the sphenoid and the optic canal. According to Coppez, fracture of this type is observed in cases in which the head is crushed by the wheel of an automobile or carriage. The contents of the orbit are badly injected and pushed forward. This produces avulsion of the globe and stretching of the optic nerve. The latter ruptures at the anterior orifice of the optic canal if the attachment of the nerve to the canal remains fast. If, on the other hand, the canal is fractured, the nerve is loosened and tears at the level of the chiasm. This demonstrates that the chiasm is more fragile than the optic nerve. Traction on the nerve results not in rupture of the nerve trunk but rather in avulsion at the level of the chiasm. Coppez [13] reproduced this type of lesion experimentally by pulling out an eyeball with its attached nerve after freeing the adhesions in the optic canal. Under these circumstances the chiasm is torn transversely.

3. As a result of fracture of the petro-occipital junction directed toward the sphenopetrosal junction. According to Coppez, such fractures were studied, especially by Bollack,[15] from the standpoint of the chiasmatic syndrome. The fracture tends to run parallel to the axis of the petrous bone, often reaching the sella turcica from behind forward and from the lateral toward the mesial border. It is perpendicular to the optic nerve on the same side. One must assume that the optic nerve is violently stretched by separation of the bone. This separation occurs in the direction of the nerve. It may be assumed that the nerve is violently pulled by the spread of the bone, the force then being transmitted to the chiasmal fibers, which are torn transversely (fig. 7). Clinical examination tends to support this view in cases of fracture of the petro-occipital or the sphenopetrosal bones.

15. Bollack, cited by Coppez.[13]

The hydrodynamic force of a displaced third ventricle must be given consideration. I have seen two cases (cases 6 and 9) in which the chiasmal lesion followed a depressed fracture of the vault. The force was applied above and must have been transmitted directly to the chiasmal region with something of a contre-coup effect. At least, the chiasm must have been forced against the underlying sella. In addition, injury to the infundibulum may occur concurrently, with resultant symptoms of diabetes insipidus. Splinters of bone projecting from the floor of the skull and causing direct injury to the chiasm are so rare that they need not be given serious consideration.

Fig. 7.—Transverse tearing of both optic nerves at the chiasm produced in the cadaver by wide separation of the skull in the petrosphenoid region. Such lesions do not occur clinically. (After Coppez.[18])

INJURIES TO THE OPTIC TRACTS

After the World War, abundant human material was provided for studying the cortical visual centers and their associated tracts. Particularly was this true in cases of gunshot wounds of the occipital lobes, in which both the position of the missile and its tract were known. Extensive observations were made by Fleischer and Ensinger,[16] Beau-

16. Fleischer, B., and Ensinger, T.: Homonymhemianopische Gesichtsfeldstörungen nach Schädel- spez. Hinterhauptschüssen, Klin. Monatsbl. f. Augenh. **65**:181, 1920.

vieux,[17] Holmes and Lister,[18] Holmes,[19] Scarlett and Ingham[20] and many other authors.[21] Studies by Fox and German[22] and by Penfield, Evans and MacMillan[23] following complete or partial lobectomies of the temporal or occipital lobe afforded excellent opportunities for perimetric observations which had been anatomically and physiologically controlled.

Holmes[19] summarized his conclusions as follows:

1. The upper half of each retina is represented in the dorsal, and the lower in the ventral part of each visual area. 2. The centre for macular or central vision lies in the most posterior part of the visual areas, probably on the margins, and in the lateral surfaces of the occipital poles. The macula has not a bilateral representation. 3. The centre for vision subserved by the periphery of the retinae is situated in the anterior portions of the visual areas, and the serial concentric zones of the retinae from the macula to the periphery are probably represented in this order from behind forwards in the visual areas. 4. Those portions of the retinae adjoining their vertical axes are probably represented in dorsal and ventral margins of the visual areas, while that in the neighborhood of the horizontal axes is projected onto the walls and the floor of the calcarine fissures. 5. Severe lesions of the visual cortex produce complete blindness in the corresponding portions of the visual fields, or, if incomplete, an amblyopia, color vision being lost, and white objects appearing indistinct: or only more potent stimuli, such as objects moved sharply, may excite sensations. 6. The defects of vision in the fields of the two eyes are always congruous and superimposable, provided that no disease or injury of the peripheral visual apparatus exists. 7. Lesions of the lateral surfaces of the hemispheres, particularly of the posterior parietal regions may cause

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17. Beauvieux: Les troubles visuels dans les blessures par coup de feu de la sphère visuelle corticale ou des radiations optiques, Arch. d'opht. **35**:410, 458, 560 and 617, 1916-1917.

18. Holmes, G., and Lister, W. T.: Disturbances of Vision from Cerebral Lesions, with Special Reference to the Cortical Representation of the Macula, Brain **39**:34 (June) 1916.

19. Holmes, G.: Disturbances of Vision by Cerebral Lesions, Med. Press Circ. **104**:490 (Dec. 26) 1917.

20. Scarlett, H. W., and Ingham, S. D.: Visual Defects Caused by Occipital Lobe Lesions, Arch. Neurol. & Psychiat. **8**:225 (Sept.) 1922.

21. Meyer, A.: The Connections of the Occipital Lobes and the Present Status of the Cerebral Visual Affections, Tr. A. Am. Physicians **22**:7, 1907. Allen, I. M.: A Clinical Study of Tumors Involving the Occipital Lobe, Brain **53**:194, 1930. Horrax, G., and Putnam, T.: The Field Defects and Hallucinations Produced by Tumors of the Occipital Lobe, ibid. **55**:499, 1932. Traquair, H. M.: Fields of Vision in Intracranial Lesions, Brit. M. J. **2**:229, 1933. Brouwer, B.: Projection of the Retina on the Cortex in Man, A Research Nerv. & Ment. Dis., Proc. **13**:529, 1934.

22. Fox, J. C., Jr., and German, W. J.: Observations Following Left (Dominant) Temporal Lobectomy, Arch. Neurol. & Psychiat. **33**:791 (April) 1935.

23. Penfield, Wilder; Evans, J. P., and MacMillan, J. A.: Visual Pathways in Man with Particular Reference to Macular Representation, Arch. Neurol. & Psychiat. **33**:816 (April) 1935.

certain disturbances of the higher visual perceptual functions with intact visual sensibility, as loss of visual orientation and localization in space, disturbance of the perception of depth and distance, visual attention loss, and visual agnosia.

Scarlett and Ingham [20] concluded:

1. Fixation of vision and normal visual acuity . . . are commonly retained when lesions of the occipital lobes have caused a complete homonymous hemianopsia. (When) . . . both occipital lobes were injured, visual acuity was reduced in both eyes . . . No disturbance of fixation was demonstrated even in these cases.

2. The hemianopic fields commonly approached to within a fraction of 1 degree of the fixation point.

3. Evidence that macular vision is represented in the apex of the occipital lobe is furnished . . .

4. Defects of the visual fields, scotomas or hemianopias, resulting from lesions of the occipital lobes, are roughly symmetrical but not exactly superimposable.

5. Greatly reduced visual perception in homonymous fields (incomplete hemianopia) may exist as a permanent residual result of occipital injury . . . In such cases bright lights and large moving objects can be discerned in fields which are blind to the usual tests for form and color.

Ingham and Lyster [24] reported the case of a patient who was under my observation at the Los Angeles County Hospital. This patient, a man aged 27, had sustained a gunshot wound in the occipital region, having been shot from behind while driving his automobile. He experienced a flash of light followed by momentary blindness. Vision quickly returned; however, he could only see above the horizontal plane but not below it. He could not see the road and turned the wheel over to his wife. He was not unconscious at any time. On his admission to the hospital a gunshot wound was found rather high in the midoccipital region. A depressed fracture was present, and the bullet was flattened near the junction of the lambdoid and the sagittal suture (fig. 8). Dr. Eliot Alden removed the bullet with the depressed fragment of bone and found the dura to be intact. This patient presented a typical bilateral inferior hemianopia on rough tests. The fields above the horizontal plane were normal. Central vision was good. Small test objects were not recognized in the lower half of either visual field until they approached the horizontal plane. Large objects could be seen 40 degrees below the fixation point. The two fields were symmetrically affected. The case illustrated the following points emphasized by Ingham and Lyster: "(1) the subjective flash of light perceived at the instant of the injury to the occipital cortex; (2) symmetrical horizontal inferior hemianopia resulting from a presumably superficial lesion of both occipital lobes close to the midline, about 6 cm. from the apexes of

24. Ingham, S. D., and Lyster, T. C.: Abnormalities of the Visual Fields, J. A. M. A. **82**:17 (Jan. 5) 1924.

the lobes, and (3) absence of the common general symptom of cerebral concussion." The patient left the hospital before perimetric studies could be made.

TEMPORARY BLINDNESS FOLLOWING CONCUSSION

Instances of temporary blindness following injury to the back of the head may be cited. Baldwin [25] reported a case of a patient who sustained a gunshot wound of the right occipital region, the bullet passing to the left occipital lobe. At operation the right occipital lobe showed wide disorganization of brain tissue with hemorrhage, a piece of bone being extracted from the left occipital lobe. The bullet was not removed. Immediately after the injury the patient was totally blind and the pupils were dilated and fixed. Three days later he began to see slightly; the pupils were small and responded to light. Two months

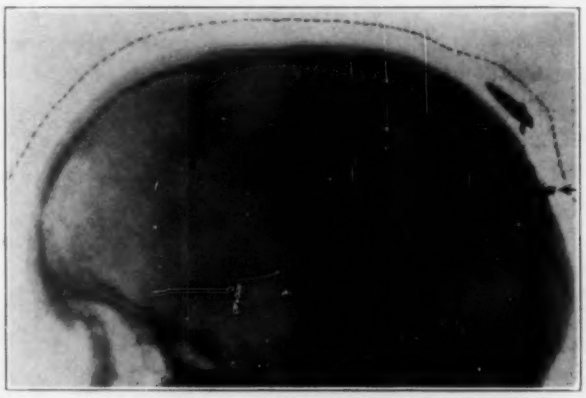

Fig. 8.—Depressed occipital fracture with a flattened bullet in the upper part of the occipital region. Lower homonymous hemianopia resulted. (After Ingham and Lyster.[24])

later vision returned in the right upper homonymous quadrant, and six months later there was homonymous hemianopia, with normal acuity and no changes in the fundi. Anderton [26] reported the case of a 9 year old child who was kicked in the forehead by a horse. He remained completely conscious but became totally blind, not even having perception of bright light. The pupils remained equal and reacted quickly. Two hours later perception of light returned; four hours thereafter

25. Baldwin, H. C.: Brain Injuries. 1. Gunshot Wound Involving Both Occipital Lobes: Study of Visual Fields. 2. Fracture of Skull: Injury to Frontal Lobe, Boston M. & S. J. **154**:185, 1906.

26. Anderton, G.: Temporary Blindness After Concussion, Brit. M. J. **2**:1005 (Nov. 28) 1925.

the patient could see moving objects, and by the next morning he had completely regained his vision. It was concluded that the injury was a localized cerebral concussion due to contre-coup violence affecting the visual centers of both occipital lobes. Newmark [27] reported the case of a 21 year old prize fighter who was struck on the jaw and fell on the back of his head. No fracture of the skull was demonstrated, but right hemianopia and astereognosis developed and a Babinski sign appeared bilaterally. Hearing was impaired on the right side. Seven days later the patient seemed completely blind but persisted in saying that he could see. Three weeks later he could see moving objects, and six weeks later he could count fingers. Visual aphasia developed, the patient being unable to name colors, although he could collect colors and match them. Ultimately the central vision became good, although the fields remained contracted. It was the impression that in cases of softening of both occipital lobes temporary amaurosis is more common than permanent blindness, and in cases of visual aphasia the patient may be unconscious of his blindness. In some cases one would suspect that in a minute circle around the fixation point there remained sensibility to light. A functional element in this case was suspected. I recently observed a case of an almost identical condition in which vision was regained within forty-eight hours.

Newmark [27] cited the case of a 4 year old boy who was struck by an automobile and in whom a hematoma of the occiput developed. He remained unconscious for three days. There was a linear fracture of the occipital bone. When the patient regained consciousness, he was blind. There was no return of vision for six months; then central vision appeared and seemed good. The fields were narrow. Two years later the fields were markedly contracted, and the fundi, which at first were said to be normal, showed pallor of the optic disks, the right disk being more affected than the left. Newmark also referred to a case of Hirsch,[28] that of a 12 year old boy who sustained a blow between the lambda and the external occipital protuberance. No fracture resulted. There was immediate complete amaurosis. All sensibility to light was absent, although the pupils reacted sluggishly to light and the fundi remained normal. Three hours later the child could perceive large white objects; seven hours later he could count fingers. Right homonymous hemianopia with normal pupillary reactions appeared. Two days later the fields and the visual acuity were normal. Although

27. Newmark, L.: Blindness Following Injuries to the Back of the Head, California State J. M. **12**:183 (May) 1914; **14**:487 Dec.) 1916.

28. Hirsch, C.: Ueber passagere Rindenblindheit durch Commotio cerebri, Deutsche med. Wchnschr. **36**:1436. 1910.

transient blindness occurred, the hemianopia was considered hysterical. Hirsch expressed the belief that "the visual centers in both occipital lobes had been affected, the right hemianopia remaining for a while after the right occipital cortex had recovered." I agree with Newmark in assuming that a commotio cerebri was present, for the restoration of vision was more rapid than would have been the case if a hemorrhage had occurred.

Word or mind blindness does not occur as frequently as one might expect. Gibson [29] reported a case of a through and through gunshot wound of the head with almost total destruction of the primary visual cortex to the mesial aspect of the left occipital lobe, specially involving the calcarine fissure and cuneus and causing some injury to the visual cortex of the right side. Right homonymous hemianopia developed. The fundi were normal. The patient apparently had visual agnosia. He did not know the nature of most objects, although he avoided them. Some were recognized imperfectly. By the aid of his eyes he could pick up comparatively small objects from the floor, but he did not know what they were until he felt them. He did not know his wife when he met her on the street, nor could he tell a man from a woman by sight. He had attacks of complete blindness, sometimes lasting for a day; these were thought to be epileptic. Gibson concluded:

> The images formed on each retina are no doubt perfect and the messages from the retina are carried to the visual cortex, but they are not received by the practically destroyed left primary visual cortex and are imperfectly recognized by the injured right primary visual cortex. He is word-blind, letter-blind and partly object-blind. The right visual cortex in right handed people does not recognize word pictures and perhaps not letter pictures, but it apparently recognizes objects as such except when injured as in this man.

ALTERATIONS IN THE FIELDS DUE TO HYSTERIA

It is not my purpose to discuss in detail the various alterations in the fields due to hysteria following head injuries. In my experience, they are more commonly met with than alterations having a true organic background. This is not strange when one remembers the diversity of symptoms of hysteria which occur after industrial injuries. Peter [30] regarded the changes in the visual fields shown in hysteria as being due to inhibition or loss of will power on the part of the patient. This results in the patient's not responding normally to usual stimuli. Whether this is due to failure of the retinal sense organs in receiving impressions or to failure of the central end-organs to stimulate consciousness is

29. Gibson, J. L.: Bullet Wound Injury to Visual Cortex on Each Side, M. J. Australia **1**:86 (Jan. 24) 1925.

30. Peter, L. C.: The Principles and Practice of Perimetry, Philadelphia, Lea & Febiger, 1931, p. 265.

questionable. He mentioned cases cited by Binet and Janet, as quoted by de Schweinitz, of patients suffering from hysterical blindness who have been hypnotized. When the hypnotic state was induced such patients could recall what they saw during the period of alleged amaurosis. This experience is used as an argument tending to support the theory of integrity of the sensory end-organs.

Many analogies may be drawn both from the general sensory patterns and from the alterations in the visual fields produced by hysteria. Anesthesia and hyperesthesia of the skin find their counterpart in the retina, as shown by amblyopia, amaurosis or scotomas. These may be bilateral or unilateral. Peter stated: "It is well to emphasize the fact that no part of the visual pathway enjoys immunity in hysteria, and that any variation of the field observed in organic disease of the visual tract may be found in hysteric disease." Three types of changes in the fields are especially characteristic: "(1) Concentric contraction of fields, with or without central amblyopia; (2) tubular fields; (3) reversal of color fields." Concentric contraction most frequently is of circular shape, and the field may be limited almost to the center of vision. Usually the fields for form and color are almost equal in size.

The fields for color, on the other hand, may be contracted in their usual order proportionately to the reduction in the fields for form, as seen in cases of optic neuritis. The eyegrounds, of course, are normal. Tubular fields leave no doubt as to the diagnosis of hysteria. Ordinarily, as the distance between the patient's eye and the screen is increased, the contracted field enlarges; in cases of tubular vision a field of the same size may be obtained at any distance. This is said to occur in cases of malingering as well as in cases of hysteria. Reversal of the fields for color and interlacing, especially in conjunction with concentric contraction or tubular vision, is characteristic of hysteria. Various types of oculomotor palsy may occur in cases of hysteria. Photophobia may likewise occur, probably expressing any analogy to hyperesthesias of the skin as shown in this condition.

REPORT OF CASES

CASE 1.—*Rupture of the left eyeball; paracentral scotoma of the right visual field following a blow across the bridge of the nose. Commotio retinae (?).*

J. F. J., a man aged 22, married, a truck driver, was referred by Dr. John D. Gillis on March 24, 1931. The patient was injured on March 23, 1931, when a tire rim sprang back, striking him across the bridge of the nose and the forehead. He was momentarily dazed. He sustained a laceration 8 cm. long across the forehead and the bridge of the nose, a fracture of the frontal sinus and a rupture of the left eyeball. On the following day Dr. J. M. Osburn removed the eyeball.

Résumé of Complaints and Findings.—On July 24 there were headache, dizziness, complete loss of smell, pain in the right eye and right side of the face and

blurring of vision on the right side. The right pupil reacted well to light and in accommodation. The right fundus showed the margins of the disk to be clearly outlined, the veins rather full and the arteries small; there were no hemorrhages or exudates and no elevation. There was slight pallor of the disk. Rough testing showed no contraction of the visual field, but one gained the impression that the patient had a central scotoma. There was complete anosmia. Soon after the accident visual acuity in the right eye was 20/20; on July 24 it was 20/50.

On October 4 the patient still complained of pain in the right eye. He stated that objects looked as though he were seeing around a dark spot. He complained of occasional headaches, slight dizziness and no return of the sense of smell. The right pupil reacted well to light and in accommodation. The disk was somewhat paler than normal; anosmia persisted. The visual fields (fig. 9) showed a scotoma of the right eye interfering with central vision. Vision in the right eye was 20/100. The blood pressure was 120 systolic and 76 diastolic.

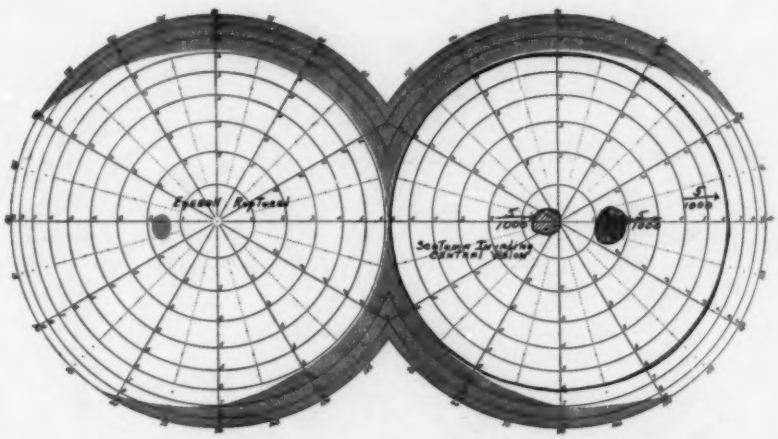

Fig. 9 (case 1).—Paracentral scotoma on the right side, presumably due to damage to the macula; uncorrected vision in the right eye was 20/100+. The left eyeball was ruptured.

Roentgenograms of the skull showed a compound comminuted depressed fracture of the anterior wall of the frontal sinus, a linear fracture through the posterior wall of the sinus and a fracture across the bridge of the nose.

Impression.—The following conditions were considered to be present: compound comminuted depressed fracture of the skull involving the frontal sinus and the bridge of the nose, rupture of the left eyeball, complete persistent anosmia, paracentral scotoma in the right visual field and slight pallor of the right disk.

CASE 2.—*Immediate monocular blindness following fracture of the left sphenoid wing and optic foramen. Subsequent recovery of an island of vision in the left lower nasal quadrant; primary atrophy of the optic nerve. Right visual field unaffected.*

A. W. B., a man aged 30, single, an attorney, was referred by Dr. Leo M. Davidoff, of New York, on Oct. 6, 1933. The injury occurred on June 18, 1933, when the patient was thrown from a horse. He had no recollection of the accident and was unconscious for about nine days.

Résumé of Complaints and Findings.—When the patient recovered consciousness he complained of complete blindness in the left eye. This eye was edematous and ecchymotic, and the pupil was enlarged. The results of ophthalmic examination were negative shortly after the accident, but later primary atrophy of the optic nerve developed on the left side. The patient suffered from the usual posttraumatic headache and dizziness. He began to recover vision in the left eye at the end of a month. Vision improved slowly but steadily.

Dr. Clifford B. Walker, ophthalmologist, on studying the patient's eyes on Oct. 10, 1933, found a normal field on the right side; on the left side there were loss of vision except for the lower nasal quadrant (fig. 10) and advanced primary atrophy of the optic nerve.

Roentgenograms of the optic foramina showed slight fracture of the left sphenoid wing, with slight narrowing of the left foramen.

Impression.—Concussion and fracture of the skull involving the left optic foramen were considered to be present. The defect in the left visual field was probably caused by direct injury to the optic nerve at the foramen.

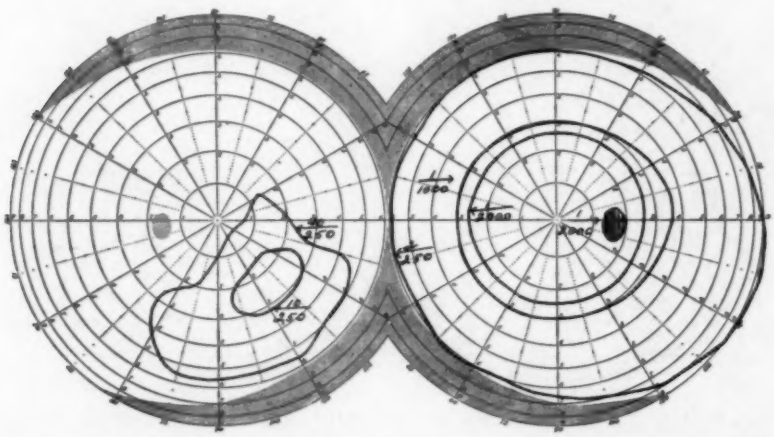

Fig. 10 (case 2).—Island of vision in the lower temporal portion of the left field, four months after a head injury. There was immediate monocular blindness in the left eye, with subsequent recovery of vision. Primary atrophy of the optic nerve occurred. The nerve was injured near the optic foramen. Corrected vision was 3/200 in the left and 20/15+ in the right eye.

CASE 3.—*Left visual field preserved only in the upper nasal quadrant; right visual field normal. Primary atrophy of the optic nerve on the left; moderate atrophy on the right.*

O. R. W., a man aged 20, single, a miner, was referred by the State Compensation Insurance Fund on July 2, 1934. He was injured on May 23, 1934, in a tunnel cave-in. He had no recollection of the accident; he recovered consciousness the following day but was irrational for several days.

Résumé of Complaints and Findings.—There were headache, dizziness, backache and loss of vision in the left eye. Both disks were clearly outlined and of normal color and showed unusually large cups. The pupils were equal and reacted well to light and in accommodation. There were numbness of the right side of the face and partial peripheral paralysis on the right side. On July 12,

1934, the visual field of the right eye showed no constriction, but there was marked loss of vision on the left side—there remained only an island of vision in the upper nasal portion of the field and there was loss of central vision (fig. 11). Repeated subsequent examinations showed relatively little change in the visual fields. Later there developed increasing pallor of both disks; this was especially marked on the left side. At the time of writing the left disk is sharply outlined, almost chalky white, and shows an appearance typical of advanced primary atrophy of the optic nerve.

Roentgenograms of the skull showed no fracture.

Impression.—The following conditions were considered to be present: concussion, peripheral facial palsy on the right side and injury to the left optic nerve near the chiasm.

CASE 4.—*Blindness in the left eye immediately after head injury. Subsequent primary atrophy of the optic nerve on the left side.*

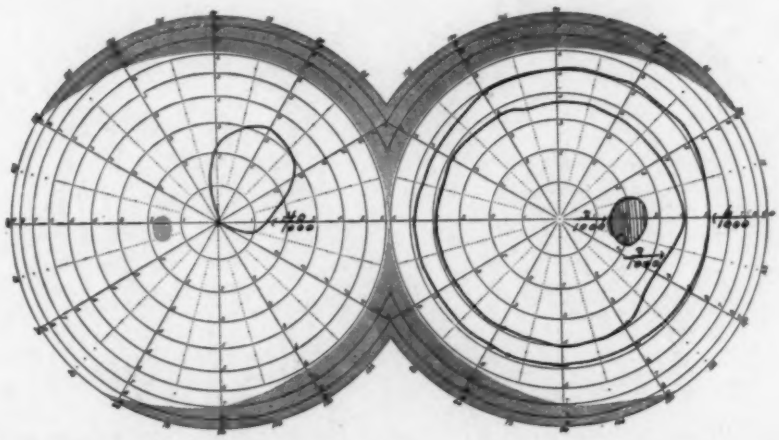

Fig. 11 (case 3).—Remaining island of vision in the upper nasal quadrant of the left field, with lowered visual acuity, after a head injury. The left optic nerve was presumably injured anterior to the chiasm. With the left eye the patient saw a person as something shadowy at 15 feet (4.5 meters); in the right eye uncorrected vision was 20/40.

H. J. F., a man, aged 35, married, a serviceman, was referred by Dr. B. C. Adams, of Riverside, Calif., on Nov. 5, 1933. The patient was injured on Sept. 29, 1933, when his car went down a bank. He recovered consciousness within a few minutes.

Résumé of Complaints and Findings.—There were: deafness in the right ear; blindness in the left eye; numbness of the left side of the face; headache and dizziness; partial anosmia in the right nostril; complete paralysis of the abducens nerve bilaterally; partial paralysis of the left trochlear and oculomotor nerves and of the right facial nerve, and motor and sensory disturbances referable to the left trigeminal nerve.

Examination of the fundus of the right eye showed that the disk was sharply outlined and rather pale, the veins were within normal limits and the arteries were small; there were no hemorrhages, exudates or elevation. In the left eye the

margins of the disk were sharply cut and pale; there was primary atrophy of the optic nerve; the veins were of moderate size; the arteries were small; there were no hemorrhages, exudates or elevation. There was complete paralysis of both external rectus muscles. Apparently the right oculomotor nerve was not involved; on the left side there was partial ptosis. The right pupil reacted readily to light directly but not consensually; the left pupil reacted to light consensually but not directly. The patient was unable to turn the left eye out and up, but he could turn it down and in. On the right side the ocular movements were essentially normal except that the patient could not turn the eye out. The trochlear nerve had apparently escaped injury on the right, but was partially involved on the left, side. There was complete blindness in the left eye; vision was good in the right. The blood pressure was 125 systolic and 80 diastolic.

Examination on Feb. 4, 1935, showed advanced primary atrophy of the optic nerve on the left side, the disk being pearly white and the arteries threadlike. On

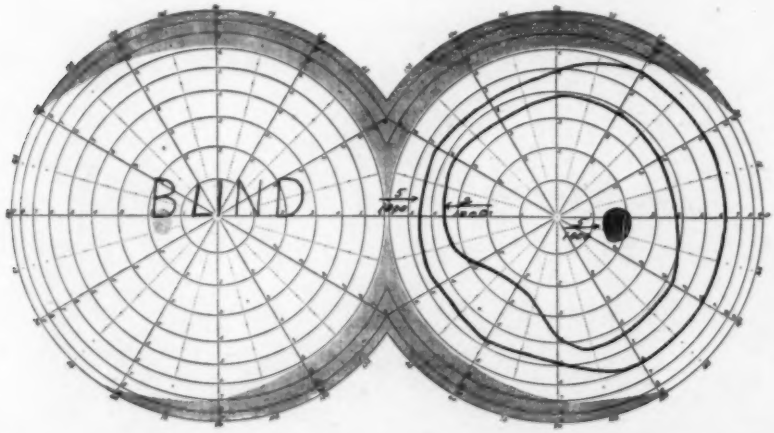

Fig. 12. (case 4).—Immediate complete blindness in the left eye, with primary atrophy of the optic nerve, probably due to injury of the optic nerve at the optic foramen. In the right eye uncorrected vision was 20/40; corrected vision, 20/30.

the right side the disk was sharply outlined, the optic cup was distinct, the veins were of good caliber, the arteries were small and the disk was somewhat paler than normal. The pupils were unequal, the left pupil being larger than the right. The left pupil did not react to light but reacted consensually. The right pupil reacted quickly to direct light but did not react consensually. Hypesthesia to touch over the entire distribution of the left trigeminal nerve and corneal anesthesia persisted. Hearing was diminished on the right side. Weber's test showed the sound referred to the right. Determination of the visual fields showed complete blindness on the left and an approximately normal field on the right side (fig. 12).

Roentgenograms of the skull showed a linear fracture in the right temporal region.

Impression.—The disturbances were regarded as being due to injury to the left optic nerve at the optic foramen, resulting in monocular blindness and primary atrophy of the optic nerve. There was involvement of other cranial nerves.

CASE 5.—*Blindness in the left eye following a gunshot wound of the head.*

J. M., a Mexican man aged 38, married, a laborer, entered the Los Angeles County Hospital on Jan. 13, 1919, and was again seen in January 1935. The patient had sustained a gunshot wound in the left temple.

Résumé of Complaints and Findings.—There were complete paralysis of the oculomotor nerve and complete blindness in the left eye. The blood pressure was 136 systolic and 88 diastolic. The Wassermann reaction of the blood was negative.

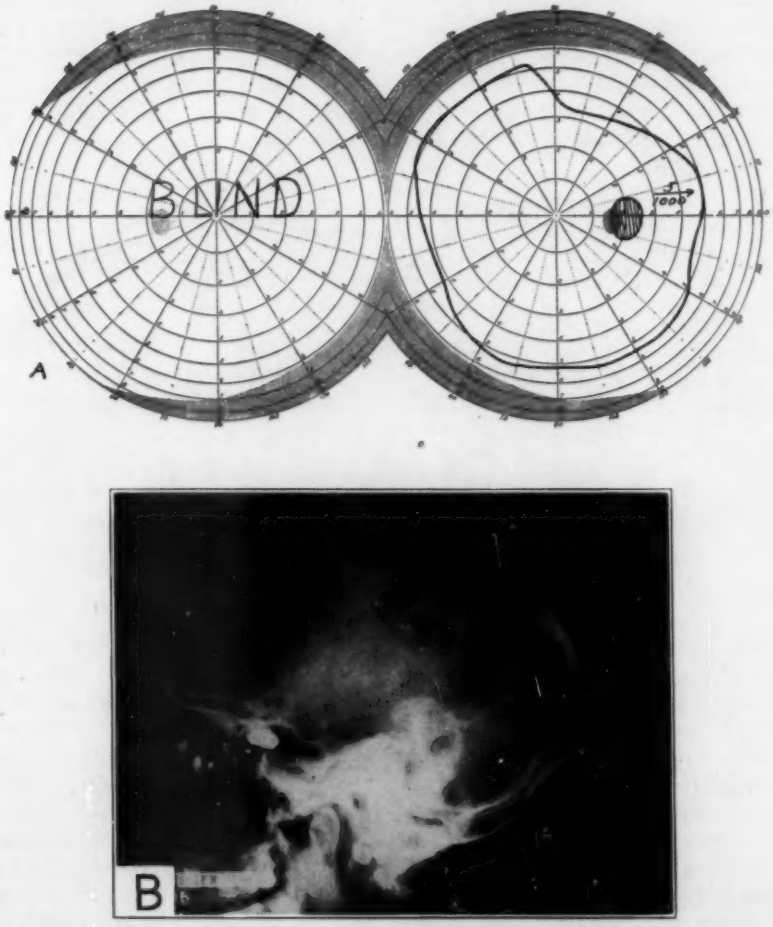

Fig. 13 (case 5).—*A*, immediate blindness in the left eye following a gunshot wound of the head. The left optic nerve was severed. *B*, roentgenogram showing the position of the bullet near the chiasm.

Roentgenograms made in 1935 showed a metallic foreign body resembling a deformed bullet lying in the median wall of the left orbit, in the region of the sphenoid sinuses. A trail of metallic fragments extended forward toward the base of the nasal bones. The main portion of the bullet lay immediately anterior to the sella turcica and somewhat toward the left. (The report on the roentgen examination was given by Dr. R. W. Johnson.)

Determination of the visual fields made on Jan. 25, 1935, showed complete blindness in the left eye and moderate contraction of the upper temporal portion of the field on the right side (fig. 13).

Impression.—The disturbances were considered to be due to a gunshot wound of the head, resulting in severance of the left optic nerve by a bullet.

CASE 6.—*Blindness in the left eye, temporal hemianopia on the right side following a blow on the head. Bilateral primary atrophy of the optic nerve.*

E. S., a man aged 26, a rotary helper, was referred by the State Compensation Insurance Fund on Dec. 14, 1928. He was injured on Oct. 13, 1928, when he was struck on the top of the head by a falling elevator link. He sustained an extensive compound comminuted depressed fracture of the skull. Operation was performed soon after by Dr. Robert W. Wilcox, of Long Beach, Calif. The brain was found to be lacerated. Convalescence was slow.

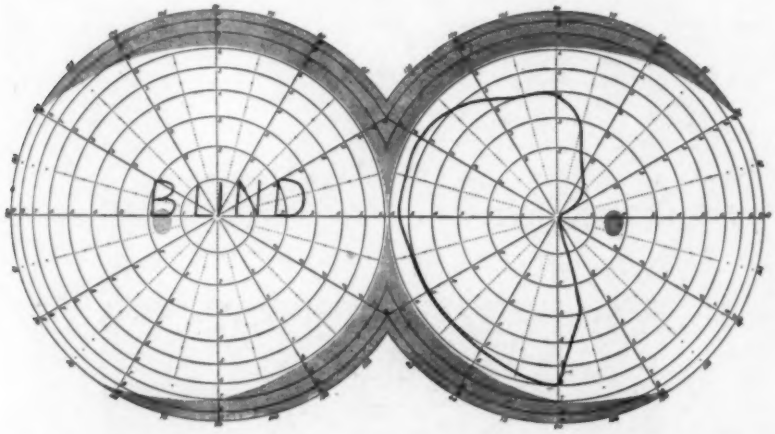

Fig. 14 (case 6).—Total blindness in the left eye and temporal hemianopia in the right eye, with bilateral primary atrophy of the optic nerve. There was probably a chiasmal lesion, the chiasm being split anteroposteriorly and the left optic nerve evulsed. In the right eye uncorrected vision was 20/70.

Résumé of Complaints and Findings.—The patient was forgetful; he exhibited changes in character, such as stubbornness and refusal to eat; there was blindness in the left eye, and disturbance of vision was noted in the right eye. No headache or dizziness was present. There were complete anosmia and advanced bilateral primary atrophy of the optic nerve; the disks were sharply outlined and chalky white; the veins were of moderate size, and the arteries were small. The left pupil did not react to direct light; the right reacted quickly to light. Determination of the visual fields on Oct. 15, 1929, revealed blindness in the left eye and fairly complete temporal hemianopia in the right eye (fig. 14). A suggestion of a Babinski sign and sporadic ankle clonus were present on both sides. The depressed fracture of the skull included almost the entire forehead. There was also a fracture into both orbits, apparently injuring the optic nerves. The blood pressure was 120 systolic and 70 diastolic.

A note written on Jan. 28, 1929, by Dr. Lloyd Mills, ophthalmologist, stated: "The condition of this man's right optic nerve is such as to give much hope that

there will be no further atrophic change. The color, while a little pale, is within normal limits; the nerve is well vascularized, and there is no particular change in the caliber of the retinal vessels. Visual function seems to be excellent within the limits of the fields which have been retained. In my opinion this will be retained permanently."

Impression.—The following conditions were considered to be present: compound comminuted depressed fracture of the frontal region of the skull; concussion, contusion and laceration of the brain; fracture extending into both orbits; probably complete severance of the left optic nerve with resulting blindness; injury to the right optic nerve with resulting temporal hemianopia. It was believed that the injury to the optic nerves may have been near the chiasm.

CASE 7.—*Temporal hemianopia of left eye persisting for fourteen months after injury.*

J. W., a man aged 34, married, a specialty distributor, entered the Los Angeles County Hospital on Oct. 18, 1934. He was injured on Aug. 31, 1933, when he was struck by a shovel above the left eye.

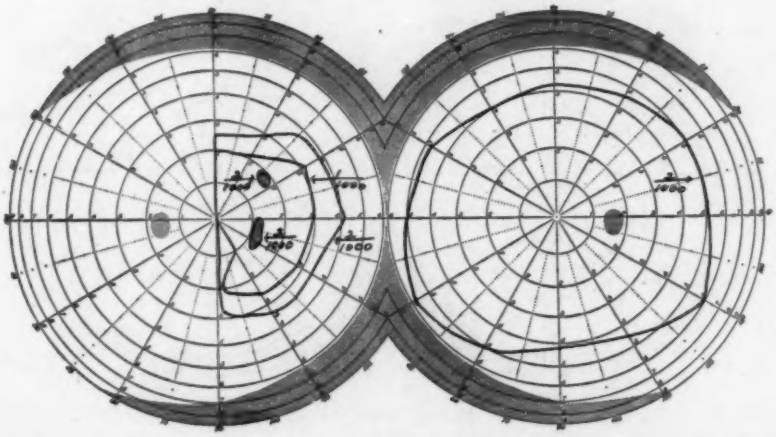

Fig. 15 (case 7).—Temporal hemianopia in the left eye subsequent to head injury, probably caused by direct injury to the left optic nerve near the optic foramen. With the left eye the patient could not count fingers at 20 feet (6 meters); in the right eye corrected vision was 20/20.

Résumé of Complaints and Findings.—The patient was unconscious for an unknown length of time. After recovering consciousness he complained of headache, dizziness, inability to see with the left eye and pain in the right side of the face. This pain had the usual characteristics of a trigeminal neuralgia and was confined to the infra-orbital distribution. Several injections of alcohol failed to give relief in spite of the fact that characteristic numbness was obtained.

Except for the changes in the visual fields and the symptoms of involvement of the left trigeminal nerve the results of the neurologic examination were negative. The left pupil did not react to direct light but reacted consensually; the right pupil reacted to direct light but did not react consensually. The fundi were normal. There were no retinal detachments. The macular region, the nerve head and the vessels were normal. Vision in the right eye was 20/20; with the left eye the patient was unable to count fingers at 20 feet (6 meters). On Oct. 21, 1933, the visual fields showed a temporal hemianopia on the left (fig. 15), which

apparently developed after the injury and was still present fourteen months later. The Wassermann reaction of the blood was negative.

Roentgenograms of the skull showed no evidence of fracture.

Drs. Beigelman, Preston and Bullis expressed the following opinion: "The lesion in reference to the pupillary disturbance must be on the intercolated fibers between the anterior corpora quadrigemina and the Edinger-Westphal nucleus on the left side. The defect in the field is probably due to a lesion of the optic nerve anterior to the chiasm on the left side."

Impression.—Injury to the left optic nerve anterior to the chiasm was considered to be present.

CASE 8.—*Complete blindness immediately following head injury. Subsequent bilateral primary atrophy of the optic nerve.*

W. E. P., a man aged 49, married, a construction foreman, was referred by Dr. Roland Cummings on Jan. 14, 1932. The patient was injured on July 6,

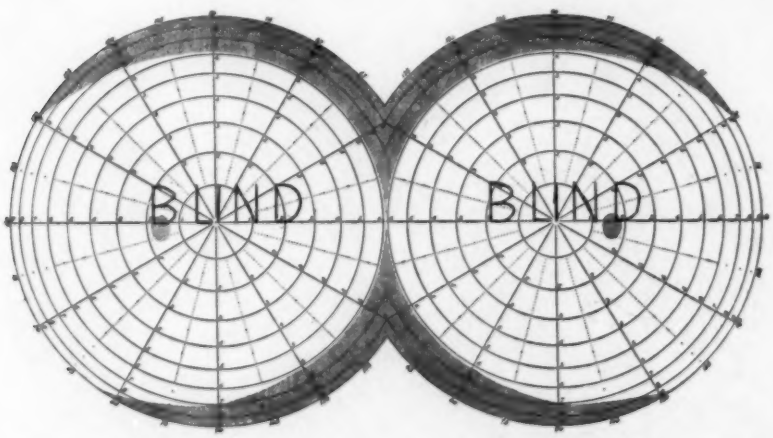

Fig. 16 (case 8).—Total blindness immediately following head injury. Primary atrophy of the optic nerves. Both optic nerves were probably severed anterior to the chiasm.

1931, when he slipped and fell under a flat car of a narrow gage railroad and was dragged about 60 feet (18 meters). He was unconscious for about two and a half hours, and when he regained consciousness he was entirely blind. He sustained bruises across the bridge of the nose and "scraped off his right ear". His eyesight was said to have been good before the injury.

Résumé of Complaints and Findings.—There was total blindness. The patient did not have the headache and dizziness so commonly present after a head injury. Examination of the fundi showed that both disks were sharply outlined and chalky white; the optic cups contained some new tissue; the veins were of good size, but the arteries were practically threadlike; the picture was typical of bilateral atrophy of the optic nerve (fig. 16). The pupils were wide, round, regular, equal and fixed to light; they reacted little, if any, in accommodation. The blood pressure was 140 systolic and 100 diastolic.

Stereoscopic roentgenograms of the skull taken in the right lateral position showed considerable cloudiness in the region of the sella turcica; the posterior

clinoid processes were hazy. No fracture of the skull was seen. Stereoscopic roentgenograms taken in the anteroposterior position failed to show a fracture of either orbit.

Impression.—The following conditions were considered to be present: concussion of the brain and immediate total blindness, probably due to severance of the optic nerves at the chiasm. (This is the only case of total blindness in this series.)

CASE 9.—*Bitemporal hemianopia, probably due to splitting of the optic chiasm anteroposteriorly, following head injury. Bilateral primary atrophy of the optic nerve of moderate degree.*

A. F., a man aged 34, married, a chef, was referred by Dr. Joseph Jacobs on Dec. 15, 1931. He was injured on Nov. 17, 1931, in a collision of his automobile and a freight train. He is said to have been unconscious for several days. He bled from the left ear and had severe headache, nausea and vomiting the first few days.

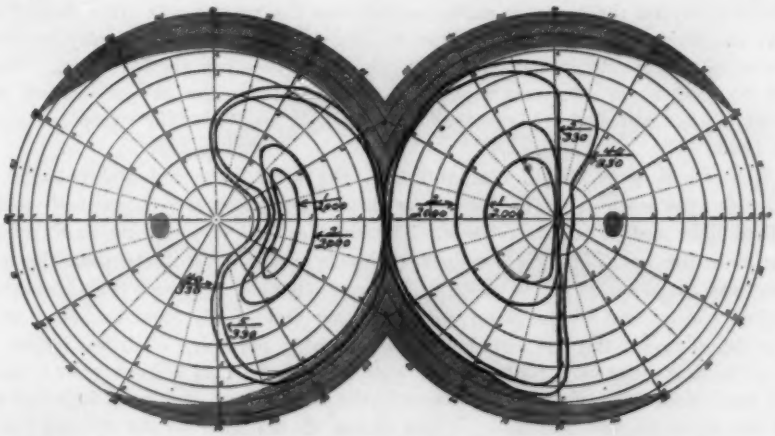

Fig. 17 (case 9).—Bitemporal hemianopia subsequent to chiasmal lesion. The chiasm was presumably split in an anteroposterior direction. Corrected vision was 20/200 in the left and 20/30— in the right eye.

Résumé of Complaints and Findings.—The patient had delusions regarding relatives, lapses of memory, difficulty in seeing, especially with the left eye, and abnormal thirst.

There were bitemporal hemianopia; diabetes insipidus, the patient drinking about 9 quarts (8.5 liters) of water a day and excreting an equal amount of urine, and mental confusion regarding the accident. The eyegrounds showed definite pallor of both disks, the picture suggesting an early stage of primary atrophy of the optic nerve, more marked on the left than on the right. The hemianopia was more complete on the left than on the right (fig. 17). The pupils were wide and equal and reacted poorly to light and in accommodation. The blood pressure was 140 systolic and 100 diastolic. The fields subsequently improved with diathermy administered under Dr. Clifford B. Walker's direction.

Roentgenograms of the skull showed a long linear fracture in the right frontal region with a slight depression.

Impression.—The following conditions were considered to be present: concussion of the brain; fracture of the right frontal region of the skull; diabetes insipidus, of traumatic origin; a chiasmal lesion, of traumatic origin; primary atrophy of the optic nerve, and bitemporal hemianopia.

CASE 10.—*Right nasal hemianopia accompanying arteriovenous aneurysm of the right internal carotid artery and cavernous sinus, appearing approximately three months after injury.*

A. H. L., a woman aged 46, married, a teacher, was referred by Dr. J. M. Nielsen on March 2, 1934. She was injured on Oct. 2, 1933, when she was struck by an automobile. She remembered being struck and thrown through the air, but she did not remember striking the pavement. She regained consciousness shortly afterward. She sustained a laceration of the scalp.

Résumé of Complaints and Findings.—The patient complained of generalized increasing headache; she was never free from discomfort in the head; she had attacks of sharp pain behind the right eyeball and stated that there was a feeling as though the eye would pop out; there was no observable bulging of the eye. The pain behind the eye was more severe when the patient was lying down; she slept propped up. Three months after the accident she noticed difficulty in vision consisting of blurring in the right eye; this increased when she lay down. There was no disturbance of vision in the left eye. At times the patient bumped into things on her left side. There was no ringing in the right ear except noises in the head.

Both fundi were within normal limits; the veins were full and pulsated on each side; the margins of the disks were clear. The pupils were equal and reacted well to light and in accommodation. The right eyeball was slightly more prominent than the left. The right palpebral fissure was a little wider than the left; there was no pulsation of the eyeball. When the patient lay down she experienced marked constriction of the nasal portion of the right field, almost amounting to nasal hemianopia; the left visual field was roughly normal. With the patient in the recumbent position a tongue blade (numbered from 1 to 9 from left to right) was held before her right eye. She saw the numbers on the right half but did not see those on the left half. When sitting up she saw all the numbers with the right eye until one compressed both jugular veins. When this was done she could no longer see the numbers to the left, but those to the right continued to be visible. When the right jugular vein alone was compressed she slowly lost sight of the numbers on the left end of the stick. If compression was firm enough to cut out the right carotid artery as well as the right jugular vein, there was no loss of vision. Similar tests carried out on the left side showed no disturbance of vision. Figure 18 shows the condition of the visual fields before and during compression of the jugular veins. The blood pressure was 140 systolic and 90 diastolic.

Roentgenograms of the skull showed no evidence of fracture. Dr. Blaine reported: "In the oblique position note is made of a definite difference in the size and shape of the optic foramen; the right one presents normal features on roentgen examination, while the left one is much larger than normal; there appears to be a bony density at the upper posterior quadrant of the right foramen, the exact significance of which I do not know but which suggests an enostosis."

Jan. 9, 1935, Dr. Nielsen stated that about six weeks subsequent to our examination the patient suffered from hiccup. She lay on her face in bed and held her breath. This was followed by intense pain behind the right eye and a noise in

the head. The right eye became more prominent and remained so for a number of weeks. Subsequently the subjective murmurs in the head disappeared; the eyeball receded, and the aforementioned visual disturbances cleared up.

Impression.—Posttraumatic arteriovenous aneurysm of the left internal carotid artery and the cavernous sinus was considered to be present.

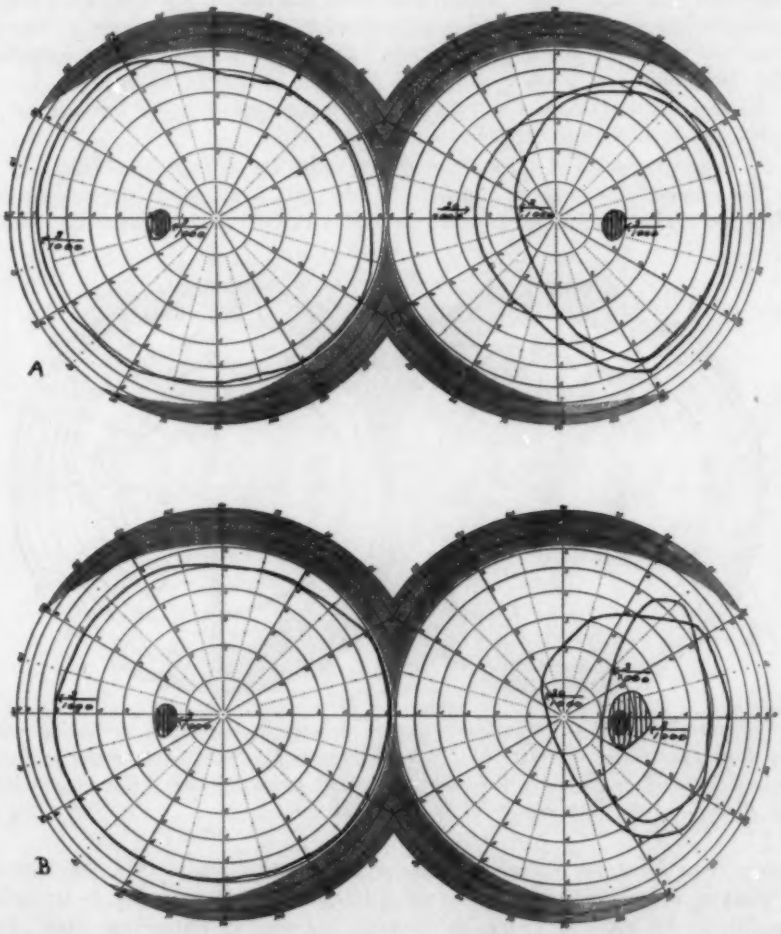

Fig. 18 (case 10).—*A*, nasal contraction of the field of the right eye subsequent to traumatic arteriovenous aneurysm when no compression was applied to the jugular veins; *B*, marked increase of the visual defects following compression of the jugular veins. Vision was 20/20+ in both eyes.

CASE 11.—*Right homonymous defects following extradural hemorrhage on the left side; subsequent improvement.*

J. C., a schoolboy aged 6, was referred by Dr. Hugo M. Kersten on Sept. 12, 1930. He was injured on Sept. 9, 1930, when he fell from a swing at school.

Résumé of Complaints and Findings.—The patient was unconscious for a short time immediately after the injury. On September 11 he became comatose and convulsions beginning in the right hand developed.

Examination disclosed weakness of the right hand. The pupils were unequal, the left pupil being larger than the right; both reacted to light. The eyegrounds showed overfilling of retinal veins, and the margins of the optic disks were somewhat obscured. The process was more marked in the left eye. On the right side there was hemiparesis, more marked in the upper extremity. The right knee jerk was more active than the left. There was a Babinski sign bilaterally. The spinal fluid was bloody.

Roentgenograms showed a long linear fracture crossing the left side of the skull from the occiput to the temple.

A large extradural clot was removed at operation on Sept. 12, 1930.

The mother first noticed difficulty in the child's vision in September 1931, when he again started school. He seemed awkward and bumped into things.

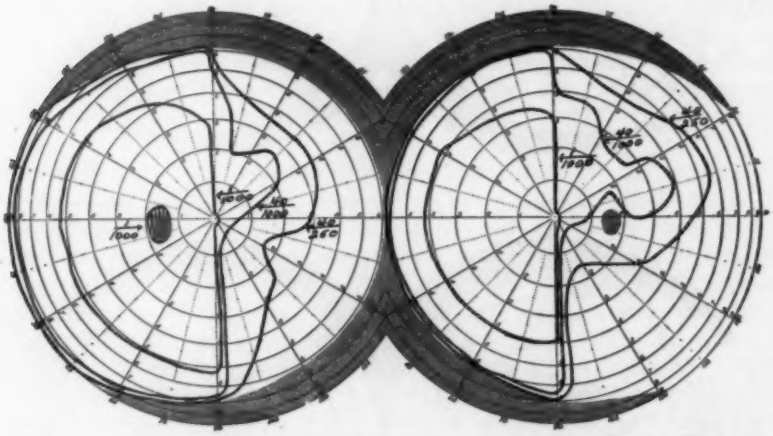

Fig. 19 (case 11).—Right homonymous defects in the fields persisting more than four years after evacuation of a large extradural hematoma on the left side. Probable secondary subcortical lesion of the left temporal lobe. Corrected vision was 20/20— in the left and 20/15 in the right eye.

Glasses were fitted, but no improvement occurred. On Oct. 1, 1934, Dr. Clifford B. Walker, ophthalmologist, discovered a right homonymous defect in the fields (fig. 19). I did not observe the defect while the child was under my care. This is not surprising, as the child was acutely ill at first and was too young to complain of moderate visual disturbance.

Impression.—The following conditions were considered to be present: linear fracture of the skull and interval hemorrhage on the left side. It is probable that a second subcortical clot existed in the left temporal lobe.

CASE 12.—*Right lower homonymous defects in the fields following a blow on the head. Negative findings at operation.*

J. C., a Mexican man aged 23, married, a laborer, was admitted to the Los Angeles County Hospital on Nov. 1, 1934, after being struck with the butt of a revolver over the right temple.

Résumé of Complaints and Findings.—On admission the patient was stuporous. The right pupil was dilated and static; the left was mobile. There was moderate spasticity on the left side, all the deep reflexes on the left being more marked than those on the right. The spinal fluid was bloody and was under increased pressure. The Wassermann reaction of the blood and that of the spinal fluid were negative. The patient improved quite rapidly and was discharged on Dec. 12, 1934. He returned on Dec. 16, 1934, complaining of inability to see with the left eye, of continuous headache in the frontal region, of dizziness and of general weakness.

Roentgenograms showed no fracture of the skull.

On Dec. 20, 1934, it was again noted that the right pupil was larger than the left; both reacted well to light. The deep reflexes on the right were increased as compared with those on the left (just the opposite of what was present on the first admission). There were a Babinski sign and a Chaddock sign on both sides.

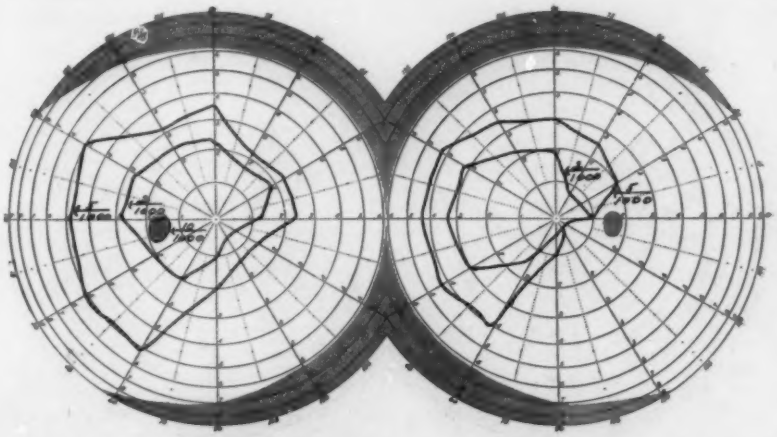

Fig. 20 (case 12).—Right lower homonymous defects in the fields subsequent to head injury. No subdural hemorrhage was encountered at operation; the defect was believed to be due to subcortical hemorrhage in the left occipital lobe. Subsequent improvement occurred. Corrected vision was 20/20 in the left and 20/70 in the right eye.

On Jan. 12, 1935, the patient had generalized convulsions, and at times he had difficulty of speech. The pulse rate dropped as low as 40. On Dec. 8, 1934, the spinal fluid was clear and colorless; the pressure was 120 mm., the cell count 2 and the Nonne test negative.

A perimetric study made on Jan. 15, 1935, showed a suspicious right homonymous contraction of the visual fields. A second study, made on Jan. 22, 1935, showed an increase of the right homonymous defect in the fields (fig. 20). During the next two weeks vision improved. On Jan. 23, 1935, multiple trephine openings were made on each side of the skull; no hematoma was discovered.

Impression.—Probably there was a chronic subdural hematoma on the left side.

CASE 13.—*Islands of vision remaining only in the upper left quadrants after head injury.*

I. P., a woman aged 20, divorced, a waitress, was admitted to the Los Angeles County Hospital on March 16, 1935. She was injured on March 5, 1935, when she fell backward, striking her head on the pavement.

Résumé of Complaints and Findings.—The patient remained unconscious for about ten minutes. She suffered from headache for a day or more; this was followed by an interval of about four days when she felt quite herself. The headache returned in the left temporal region and increased daily in severity. On about March 12, 1935, the patient noticed drooping of the left eyelid and slight weakness of the left arm and leg. During the next three days headache increased and she became stuporous.

On admission she was stuporous. There was marked palsy of the left oculomotor nerve with ptosis; the pupil was dilated and fixed, and outward rotation of the eye was noted. Marked paresis and increased deep reflexes were present on the left side. There was a Babinski sign on the left, but not on the right, side.

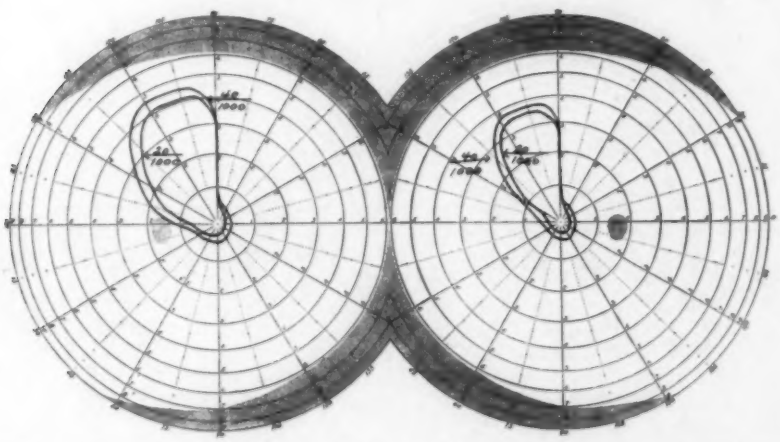

Fig. 21 (case 13).—Islands of vision remaining in the upper left quadrants. Central vision was preserved. A large subdural hematoma was evacuated on the right side; other subcortical lesions were suspected. Uncorrected vision was 6/10 in both eyes.

The spinal fluid was under a pressure of 400 mm. and was slightly bloody. The Wassermann reaction of the blood was negative. The blood pressure was 132 systolic and 86 diastolic.

Roentgenograms of the skull failed to reveal a fracture.

On March 17, 1935, Dr. R. B. Raney explored the left temporal region and found a large chronic subdural hematoma in process of formation. The contents were scooped out. A button opening was then made over the right temporal region, but no hematoma was encountered.

On March 27, 1935, study of the visual fields showed that vision remained only in the upper left quadrants (fig. 21), in other words, there was complete right homonymous hemianopia and a lower left quadrantal defect. The eyegrounds showed marked blurring of the disks, with filling of the optic cups, distention of the vessels and elevation of about 2 diopters. Visual aphasia developed. A subsequent

trephine opening over each occipital lobe failed to reveal a hemorrhage. Ventriculography showed normal-sized ventricles, which were not displaced.

Impression.—The supposition that bilateral chronic subdural hematoma was present was not borne out on exploration. Bilateral subcortical hemorrhage in the temporal or occipital lobe may have caused the picture. The probability that a chiasmal lesion existed seemed remote.

CASE 14.—*Left homonymous hemianopia more than six months after head injury. Paralysis of the left abducens nerve. Advanced secondary atrophy of the optic nerve.*

M. B., a widow aged 36, a housewife, was referred by Dr. Frank D. Sweet, of Long Beach, Calif., on Oct. 31, 1934. She was injured on Oct. 15, 1934, in an automobile collision. She remained comatose or semicomatose for a number of weeks, hospitalization being necessary for more than two months.

Résumé of Complaints and Findings.—The patient was disoriented as to time and place for several days. When the mental symptoms cleared she complained of headache and double vision. Later she complained of half vision in the left eye.

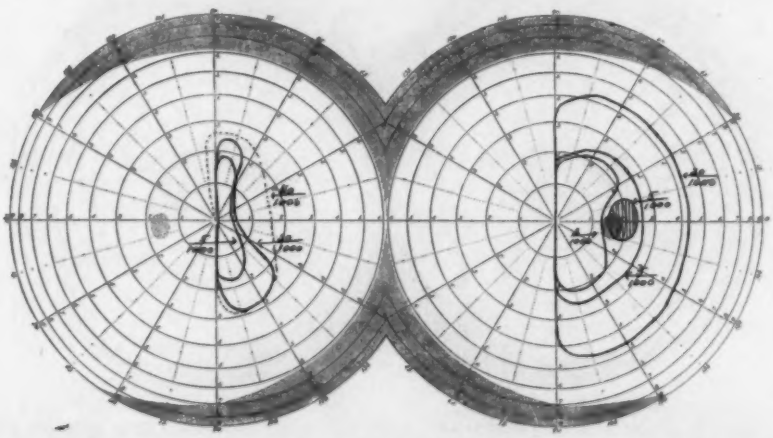

Fig. 22 (case 14).—Left homonymous hemianopia present six months after head injury. There was bilateral atrophy of the optic nerve, probably secondary. The lesion was believed to have affected the right optic tract just behind the chiasm. With the left eye the patient saw the card as something light at 20 feet (6 meters); in the right eye uncorrected vision was 20/30.

At the time of the first examination complete palsy of the left oculomotor nerve existed. The left pupil was much larger than the right one and reacted little to direct light but well consensually. There was complete ptosis of the upper lid. The left eye could not be turned outward beyond the midline, as there was complete paralysis of the abducens nerve. Vision in the left eye was low. The details of the left fundus were indistinct, but the disk seemed a little pale. The right fundus showed a clearly outlined disk, with arteries and veins within normal limits. The blood pressure was 110 systolic and 40 diastolic.

Roentgenograms of the skull failed to reveal a fracture of the vault. A suspicious line running anteroposteriorly between the maxillary antrums was noted. This may have represented a fracture.

The patient was reexamined on April 10, 1035. At that time the palsy of the oculomotor nerve had practically cleared up. The pupils, however, were still

unequal, the left being somewhat larger than the right. The left pupil reacted sluggishly to light; the right one reacted actively. There was still complete paralysis of the left abducens nerve. The right fundus showed a sharply outlined, pale disk with new tissue in the optic cup. The veins were of average size; the arteries were small. The left fundus was less distinctly seen, because of haziness of the cornea and media. The disk, however, appeared to be pale; the arteries were small. The visual fields showed a typical left homonymous hemianopia with marked contraction of the nasal field on the left. Visual acuity on the left was greatly reduced (fig. 22).

Impression.—The following conditions were considered to be present: concussion and contusion of the brain; possible fracture of the midmaxillary region; paralysis of the left abducens nerve; bilateral secondary atrophy of the optic nerve, and left homonymous hemianopia. The lesion was presumed to be in the left optic tract just posterior to the chiasm.

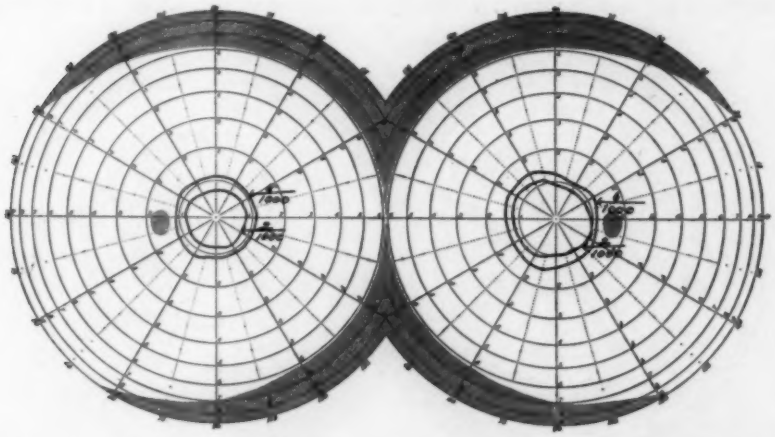

Fig. 23 (case 15).—Symmetrical contraction of the fields two months after fracture in the left temporal region. Examination was made when litigation was pending. Uncorrected vision was 20/70 and corrected vision 20/30 in both eyes.

CASE 15.—*Symmetrical contraction of the fields appearing about two months after fracture of the skull.*

A. McH., a woman, aged 65, single, a practical nurse, was referred by Dr. Cortland Myers on Aug. 22, 1934. She was injured on August 1, when she fell down a flight of stairs. She sustained a fracture of the left wrist but was not rendered unconscious.

Résumé of Complaints and Findings.—There were: dizziness, severe pain in the left side of the head, unsteadiness of gait, ringing in the left ear and photophobia.

There was tenderness in the left temporal and parietal regions. The pupils were equal and reacted well to light and in accommodation. On Aug. 22, 1934, the visual fields showed no constriction on rough tests. By October 17 they showed marked concentric constriction, which was borne out by perimetric studies (fig. 23). The patient also complained of photophobia. (A law suit was pending at this time.) The blood pressure was 195 systolic and 100 diastolic.

Roentgenograms of the skull showed a fine linear fracture in the left temporal region.

Impression.—The following conditions were considered to be present: linear fracture in the left temporal region; subsequent functional disturbance of the visual fields, probably suggested by pending litigation.

CASE 16.—*Tubular vision in the left eye following fracture of the skull. Other neurotic manifestations.*

O. W., a man aged 26, married, an oiler, was referred by Dr. R. O. Schofield, of Boulder City, Nev., on April 26, 1933. The patient was injured on May 7, 1932, when he was thrown out of a truck and rendered unconscious. He recovered consciousness seven days later. There was bleeding from the left ear. He remained in the hospital six weeks, returning to work in a tool room in August 1932. By April 1933 he was working on a power saw.

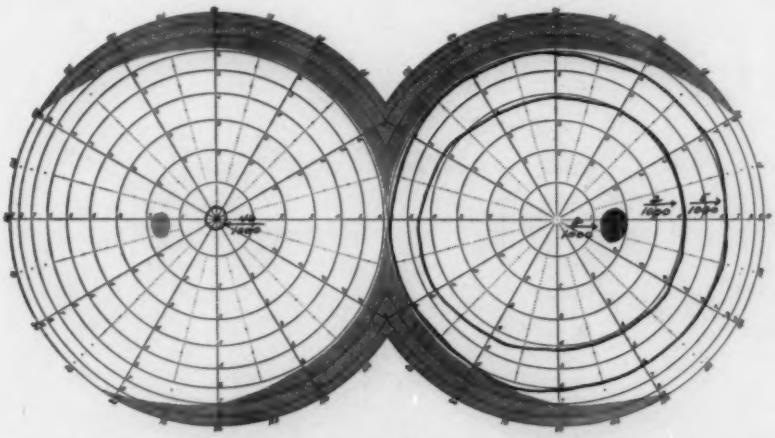

Fig 24 (case 16).—Tubular vision in the left eye (the central dot represents a large fixing object and not a scotoma) eleven months after a fracture of the skull. With the left eye the patient saw the card as something blurred at 20 feet (6 meters); in the right eye uncorrected vision was 20/30+. This patient had many other neurotic manifestations.

Résumé of Complaints and Findings.—There were pain in the back of the neck, stiffness of the neck, headache, dizziness, deafness and ringing in the left ear and blurred vision in the left eye.

There was complete bilateral anosmia. The right fundus was normal; the left could not be examined as the patient closed the eye. The pupils were unequal, the left pupil being larger than the right; both reacted to light, but the right reacted more quickly than the left. Consensual action was good in both eyes. The ticking of a watch was not heard when the watch was pressed against the left ear; it was heard at 2 inches (5 cm.) from the right ear. A tuning fork was not heard by air conduction or bone conduction on the left; air conduction was better than bone conduction on the right. Weber's test showed the sound referred to the right. The blood pressure was 130 systolic and 80 diastolic. Determination of the visual fields on April 26, 1933, showed marked hysterical contraction on the left (fig. 24).

Roentgenograms of the skull showed a fracture on the left side, beginning near the midline of the superior portion of the occipital bone, extending laterally downward and forward, crossing the parieto-occipital suture and the superior portion of the left mastoid region and entering the region of the petrous portion of the temporal bone, where it faded out.

Impression.—The following conditions were considered to be present: concussion of the brain; fracture of the skull; complete anosmia (organic); deafness in the left ear (organic), and hysterical contraction of the left visual field. The case presented furnishes an example of functional, superimposed on organic, changes.

CASE 17.—*Hysterical contraction of the fields appearing eight months after fracture of the skull.*

W. G., a man aged 26, single, a laborer, was referred by the Associated Indemnity Corporation on Sept. 12, 1934. The patient was injured on March 24,

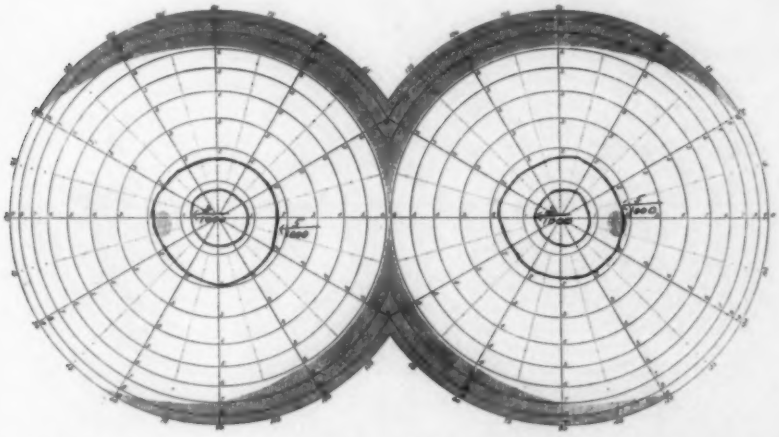

Fig. 25 (case 17).—Bilateral symmetrical contraction of the fields, probably due to hysteria, following a head injury. Many other neurotic symptoms were present. Uncorrected vision was 20/50 in both eyes.

1934, when he was thrown 10 feet (3 meters) from a tram bucket and struck his head on some rocks. He was unconscious for about six hours. Both eyes were swollen shut, and both wrists were fractured.

Résumé of Complaints and Findings.—On September 12 the patient complained of headaches, dizziness, anosmia and disturbance in taste.

Examination revealed complete anosmia. The pupils were equal and reacted well to light and in accommodation. The eyegrounds were normal. On November 21 the patient first complained of blurred vision; he could read only headlines of the newspaper. The visual fields showed symmetrically concentric contraction of a hysterical type (fig. 25). The patient was beginning to show signs of neurosis. On December 21 he still had contracted fields, but to a less marked degree. The blood pressure was 125 systolic and 60 diastolic.

Roentgenograms of the skull showed a fracture crossing both frontal sinuses, with a second line extending to the bridge of the nose and crossing the right orbit.

Impression.—Fracture of the skull and concussion of the brain were considered to be present. Changes in the field due to hysteria appeared eight months after injury.

CASE 18.—*Tubular vision appearing six weeks after head injury.*

O. E. T., a man aged 39, married, a motorcycle officer, was referred by the State Compensation Insurance Fund on Oct. 9, 1934. The patient was injured on Aug. 2, 1934, when he was thrown from his motorcycle. He did not recover full consciousness for fifteen days.

Résumé of Complaints and Findings.—On Oct. 9, 1934, the patient complained of marked dizziness and headache.

Examination revealed complete anosmia. The fundi showed overfilling of the veins and new tissue in the optic cups. The pupils were equal and reacted well to light and in accommodation; extra-ocular movements were normal. Ticking of a watch was heard 2 inches (5 cm.) from the right ear; it was not heard when

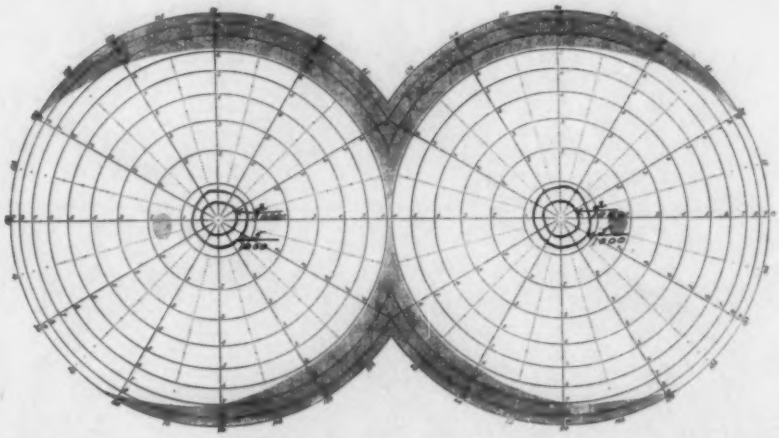

Fig. 26 (case 18).—Tubular vision present three months after a severe head injury. The patient was slightly neurotic. Uncorrected vision was 20/30 in the left and 20/20++ in the right eye.

the watch was pressed against the left ear. There was no history of bleeding from the ears. Tests with tuning forks showed that air conduction was better than bone conduction on both sides. The Weber test showed that the sound was not referred. The Romberg sign was strongly positive. All the deep reflexes were active and equal, and there were no abnormal reflexes. There was no constriction of the visual fields on rough tests. The blood pressure was 120 systolic and 80 diastolic.

On November 20 the general condition was improved, but the patient complained of watering of the eyes. Rough testing of the visual fields showed concentric contraction, which was brought out by perimetric studies (fig. 26). The fields improved when the patient returned to light work, four months later.

Roentgenograms of the skull revealed no fracture.

Impression.—The following conditions were considered to be present: concussion and contusion of the brain; anosmia; superimposed neurosis with hysterical contraction of the visual fields.

CASE 19.—*Probable hysterical contraction of the field following concussion of the brain.*

E. C., a Negro aged 32, married, a laborer, was referred by Dr. J. Rollin French on Dec. 15, 1931. He was injured on about Oct. 15, 1930, when he was struck on the top of the head by a falling iron roller. He had no recollection of the accident; retrograde amnesia was present for several hours. He was unconscious for about six hours and hospitalized for twenty days. He attempted to work two months after being injured, but stopped after one week because of severe headache.

Résumé of Complaints and Findings.—There were headaches, pain behind the eyes, burning of the eyes, blurring vision and photophobia.

The pupils were round, regular and equal and reacted sluggishly to light but well in accommodation. There was marked photophobia. The eyegrounds showed overfilling of the veins; the arteries were full; the margins of the disks were

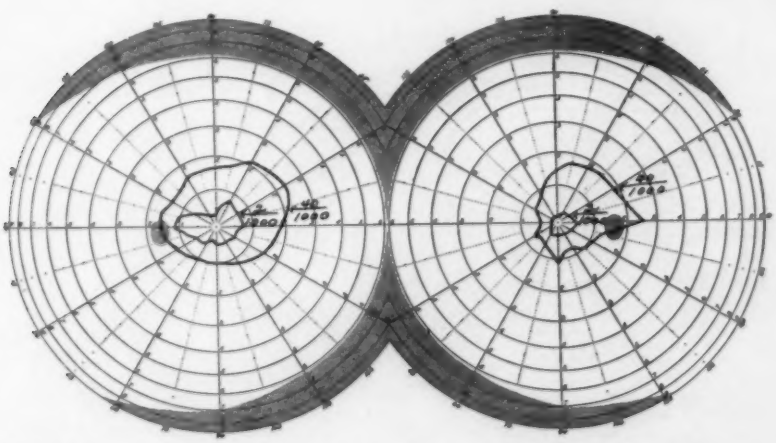

Fig. 27 (case 19).—Eccentric and generally contracted fields, the defects probably being due to hysteria. There were many other neurotic symptoms to support this diagnosis. Uncorrected vision was 20/50 in both eyes.

slightly hazy. There were no hemorrhages or exudates and no elevation. Marked contraction of both visual fields was seen by rough testing. Perimetric charting on Jan. 15, 1931, revealed marked but somewhat irregular, not typically tubular, contraction of the fields (fig. 27). Acuity of vision was diminished, being 20/50 in the left and 20/50 in the right eye. The Wassermann reaction of the blood was negative. The blood pressure was 140 systolic and 90 diastolic.

Roentgenograms of the skull showed no fracture.

Impression.—Concussion of the brain, photophobia and hysterical contraction of the visual fields were considered to be present.

CASE 20.—*Superior homonymous hemianopia, probably of functional origin, following head injury. Great fluctuation in type of fields over a period of five years.*

H. H., a man aged 41, married, a laborer, was referred by the Maryland Casualty Company on April 8, 1930. He was injured on Sept. 21, 1929, when he fell from the top of a box car, striking his head. He was unconscious for about two weeks and was hospitalized for eight weeks.

Résumé of Complaints and Findings.—There were changes in disposition, forgetfulness, impairment of hearing, headaches, dizziness and double vision.

The fundi were normal save for slight pallor of the disks. The pupils were equal and reacted well to light and in accommodation. There was diplopia on looking to the right, to the left and upward. There was bilateral deafness, greater on the right than on the left side. Tests with tuning forks showed that bone

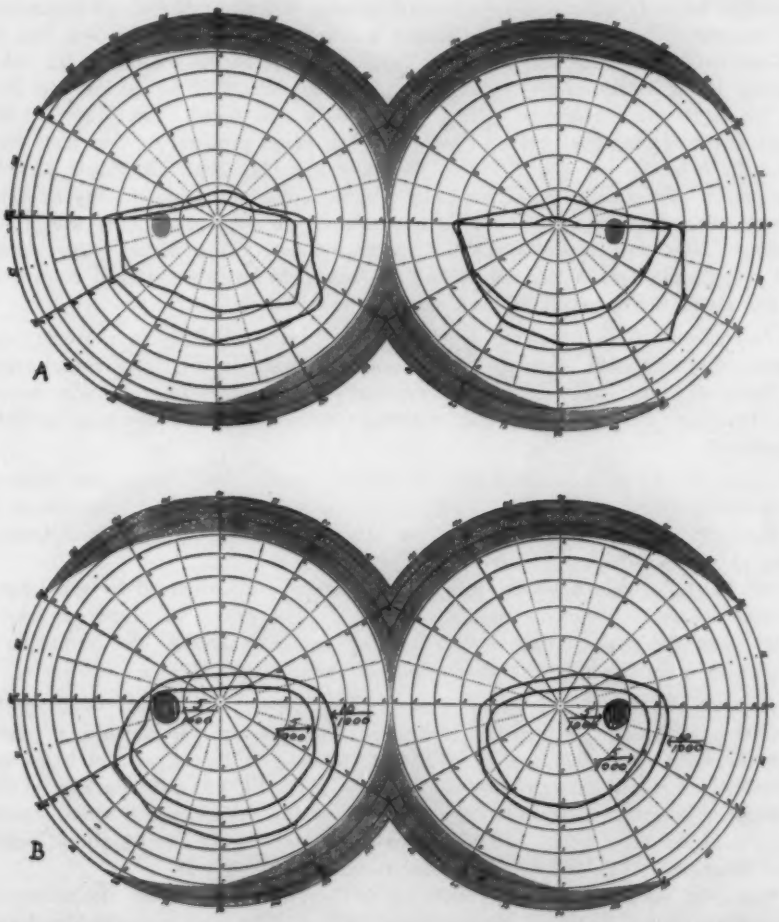

Fig. 28 (case 20).—Visual fields taken by different observers. *A*, fields in 1931; *B*, fields in 1935. In spite of the upper hemianopic defects the picture presented by the fields is believed to be due to hysteria. The development of many other neurotic symptoms supports this view. The representation of the right field in *A* was transferred from the universal perimeter. At the second examination (*B*) uncorrected vision was 20/40 in the left and 20/30 in the right eye.

conduction was better than air conduction on the right but that air conduction was better than bone conduction on the left side. The Weber test showed the sound referred to the right. The mental reactions were slow. The biceps and triceps

jerks were greater on the left than on the right side. Other superficial and deep reflexes were normal. No contraction of the visual fields was revealed by rough tests in September 1929. The blood pressure was 120 systolic and 80 diastolic. The Wassermann reaction of the blood was negative.

Roentgenograms showed an extensive T-shaped fracture in the right frontal region.

On Oct. 5, 1931, the patient was found throwing his head back and squinting; at other times he stared; he cooperated poorly. Rough tests showed constriction of the visual fields. Perimetry showed a superior hemianopia of each eye, the patient being unable to see above the midline except at the fixation point, where he saw about 3 degrees above the center. Vision was 20/50 in the left and 20/50 in the right eye. Moderate pallor of the disks was noted. On May 22, 1933, impairment of the upper fields in both eyes was again present; on that date vision was 20/70 in the left and 20/50 in the right eye (fig. 28). On April 26, 1934, the patient still complained of headache, dizziness, deafness and difficulty in seeing. There was anosmia in the left nostril but not in the right. This was a new finding. The disks were possibly paler than before. The visual fields showed not only hemianopia of the upper half of each field but also marked contraction of the lower fields, which was not present before.

Impression.—The following conditions were considered to be present: concussion and contusion of the brain; extensive fracture of the right frontal region of the skull; impairment of hearing, especially on the right side; definite changes in character and memory, and superior homonymous hemianopia, probably functional.

CASE 21.—*Central scotoma and contraction of the right visual field observed immediately after head injury. Slight macular edema and advanced arteriosclerosis of the right fundus. Subsequent inferior hemianopia of the right eye and development of manifestations of hysteria.*

W. H. L., a man aged 60, married, a salesman, was referred by the Liberty Mutual Insurance Company on Oct. 29, 1934. The injury occurred on May 9, 1934, when the patient's automobile went off an embankment. He remained in a semistuporous condition for approximately two weeks.

Résumé of Complaints and Findings.—The patient complained of headache, dizziness, impairment of memory, unsteadiness in walking and difficulty in seeing with the right eye. On June 12, 1934, Dr. John C. Williams, of San Francisco, described a scotoma in the right eye. On Aug. 28, 1934, Dr. Otto Barkan, of San Francisco, described arteriosclerotic changes of the retina and a small central scotoma in the right eye. A few patches of scotoma in the midperipheral region were described. The left field was said to be normal (fig. 29).

Suddenly, on the evening of Sept. 12, 1934 (four months after the accident), the patient lost the use of his right arm and leg, and right hemianesthesia developed. He was again able to walk at the end of a month but needed help.

There was anosmia in the right nostril. The pupils were equal and reacted well to light and in accommodation. The eyegrounds showed moderate arteriosclerotic changes but were otherwise normal. Determination of the visual fields on Oct. 29, 1934, revealed a bizarre type of hemianopia. There was complete right hemianesthesia (fig. 30). The patient used the right hand and leg awkwardly. The gait was peculiar in that he threw his right leg in front of him. In spite of awkwardness during voluntary use, involuntary gestures were made normally with the right hand. The abdominal and epigastric reflexes were not obtained. All the

deep reflexes were normal except the right knee jerk, which seemed quicker than the left. No abnormal reflexes of the Babinski type were noted. The blood pressure was 220 systolic and 120 diastolic.

Roentgenograms of the skull showed a suspicious small linear fracture in the right sphenoid region, crossing the sella.

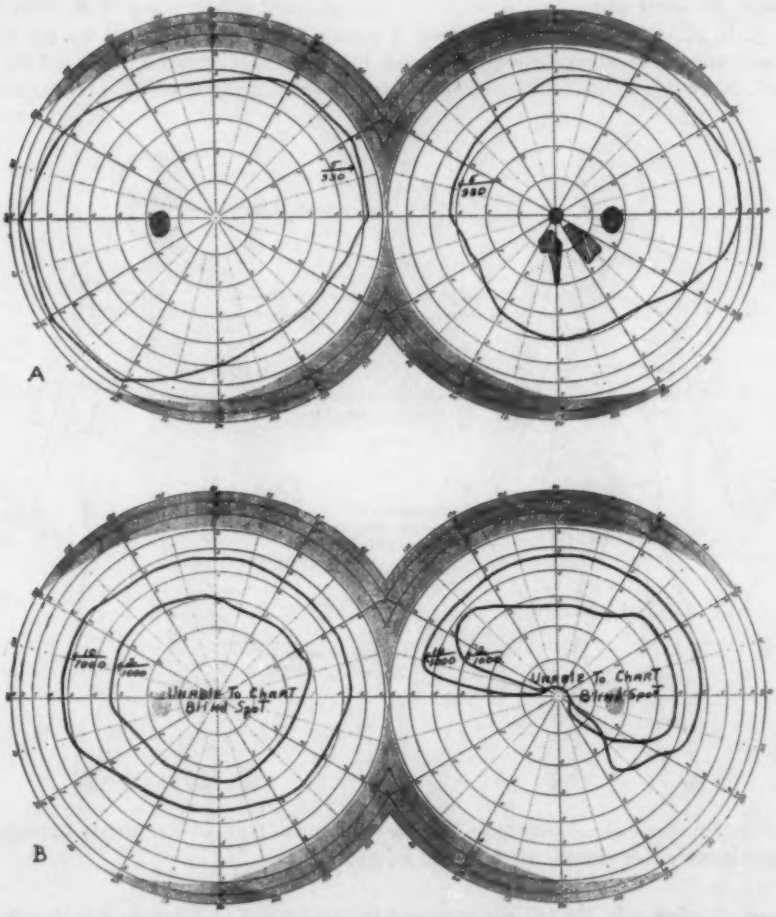

Fig. 29 (case 21).—*A*, fields showing central and paracentral scotomas on the right three months after a head injury (The representation of the right field was transferred from McHardy perimeter.) *B*, fields showing peculiar contraction on the right five and a half months after injury. Hysterical hemianesthesia appeared at about this time. At the first examination vision in both eyes was reduced to counting fingers only; at the second examination uncorrected vision was 20/30 in the left and 20/200 in the right eye.

Impression.—The following conditions were considered to be present: concussion and contusion of the brain; probable fracture of the skull. The sudden

onset of right hemianesthesia four months after injury was believed to be functional. The early changes in the field were scotomas on the right side; the later changes consisted of a bizarre inferior hemianopia. The latter was construed as a functional condition.

CASE 22.—*Moderate concentric contraction of the left visual field with other manifestations of hysteria occurring nine months after injury and coincidental with return to heavy work.*

J. S. R., a man aged 26, married, a rotary helper, was referred by the State Compensation Insurance Fund on April 19, 1934. He was injured on Feb. 11, 1934, when a derrick collapsed and he was thrown into the ocean. He sustained

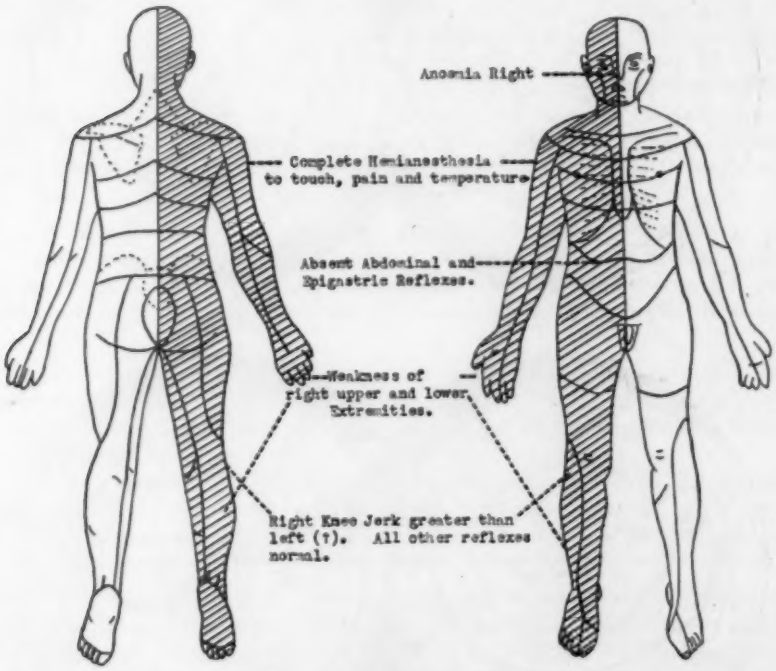
Anosmia Right
Complete Hemianesthesia to touch, pain and temperature
Absent Abdominal and Epigastric Reflexes.
Weakness of right upper and lower Extremities.
Right Knee Jerk greater than left (?). All other reflexes normal.

Fig. 30 (case 21).—Diagram showing hysterical type of anesthesia appearing approximately five months after a head injury.

a deep abrasion over the left eyebrow and left eyelid and was unconscious for about three hours.

Résumé of Complaints and Findings.—There were headaches in the left frontal region and marked dizziness on stooping or on sudden change of position. There was a scar in the left eyebrow showing the imprint of pipe threads. The pupils reacted well to light and in accommodation. The fundi were normal. The blood pressure was 130 systolic and 70 diastolic.

Roentgenograms of the skull revealed no fracture.

The patient returned to work, roughnecking, on Oct. 20, 1934, and continued working until November 6. This was heavier labor than should have been given him. Headaches and dizziness were immediately increased. There developed hypesthesia of the entire left side, including relative anosmia in the left nostril

(fig. 31). The patient also complained of blurring of vision in the left eye. Perimetric determination of the fields made on Nov. 26, 1934, showed a beginning contraction of the left field (fig. 31). The patient subsequently returned to lighter work, and the manifestations of hysteria cleared up.

Impression.—Concussion of the brain was thought to be present. The manifestations of hysteria developed nine months after the injury, when the patient was physically unable to do heavy work.

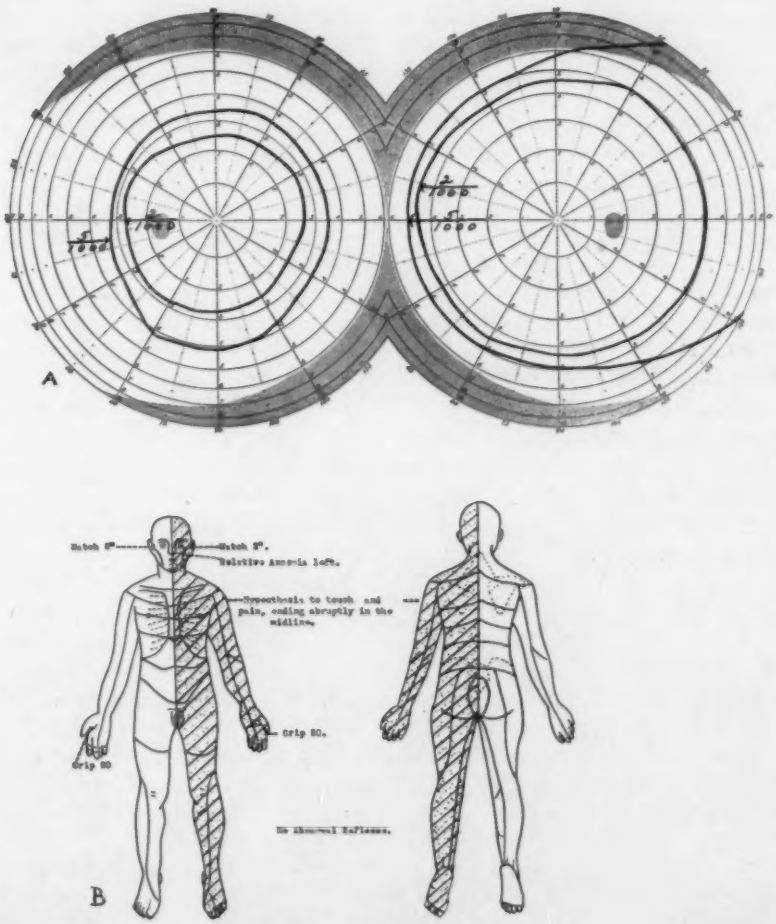

Fig. 31 (case 22).—*A*, moderate contraction of the left visual field, probably functional. Uncorrected vision was 20/30 + + in the left and 20/50 + + in the right eye. *B*, sensory changes due to moderate hysteria coincidental with alteration in the ipsilateral field. Both appeared when the patient began to do heavy labor and cleared up when his occupation was changed.

CASE 23.—*Marked contraction of the right visual field (probably hysterical) appearing approximately three days after a minor head injury.*

J. C., a man aged 46, married, a laborer, was referred by the Union Oil Company on Nov. 10, 1931. The injury occurred on Oct. 12, 1931, when the patient

bumped his head against an iron flange. He was said to have been unconscious for twenty minutes. In spite of severe headache he returned to work the following day. After working for two days he was obliged to stop. A period of headache and dizziness followed. Three days after the injury there developed blurring of vision in the right eye, as well as diplopia, which lasted ten days.

Résumé of Complaints and Findings.—There were headaches, dizziness and blurring of vision in the right eye. The fundi showed fulness of the veins, some new tissue in the optic cups and sharp disk margins. The pupils reacted well to light and in accommodation. There was constriction of the right temporal field as judged by rough tests. The abdominal and epigastric reflexes were quicker on the right than on the left. The blood pressure was 130 systolic and 80 diastolic. The Wassermann reaction of the blood was negative. The visual fields showed general constriction.

Roentgenograms of the skull showed no evidence of a fracture.

On April 29, 1933, there was severe headache. The right eye again "went blind" for a minute or two. The patient returned on May 16, 1933. He had been doing light work since January 1932. The pupils were equal and reacted quickly to light and in accommodation. The eyegrounds were normal. The abdominal and epigastric reflexes were equal. There was moderate hypesthesia to touch, pain and temperature over the entire left side of the body (fig. 32). This was a new finding. The right visual field still showed marked contraction, but there was definite improvement in the left (fig. 32).

Impression.—Moderate concussion of brain and residual manifestations of hysteria were considered to be present.

CASE 24.—*Hysterical contraction of the left visual field following fractures extending into the left orbit. Improvement nine years later.*

A. S., a man aged 51, married, a stunt actor, was referred by Dr. John D. Gillis on Nov. 3, 1923. The patient had been kicked in the head by a horse, being immediately rendered unconscious. There was bleeding from the nose but not from the ears.

Résumé of Complaints and findings.—There was a 2 inch (5 cm.) laceration in the left frontal region. After sustaining the injury the patient remained in a semicomatose condition for three or four days. A decompression was performed on November 7 and revealed a tight, wet brain. The patient remained irrational for about three weeks. His convalescence was unsatisfactory and slow. The Wassermann reaction of the blood was negative.

Roentgenograms showed an extensive stellate fracture in the left frontal region which ran down into the temporal bone and "behind the left orbit."

This patient was followed for about five years. During that time he presented many mental aberrations, changes in memory, disturbances of orientation and periods of euphoria. He insisted that he was blind in the left eye from the time that he recovered consciousness. The eyegrounds appeared essentially normal on early examination, but as time went on the left disk showed increasing pallor. Moderate advancing primary atrophy of the disk was considered to be present. Dr. Lloyd Mills, ophthalmologist, also observed the patient and in a report on an examination made on Dec. 22, 1923, described the right fundus as essentially normal. On the left he found moderate atrophy of the choroid near the terminal twigs of certain retinal vessels. He also found moderate whitening of the left optic nerve, with temporal absorption of its head. Moderate arteriosclerotic changes were evident. The central changes in the choroid were considered non-

traumatic, and it was believed that the changes in the left optic nerve would be slowly progressive. This proved to be the case.

There were marked alterations in the form fields. On August 27, 1924, there was a typical hysterical contraction of the left field (fig. 33); on Nov. 13, 1925, this field had widened, and on June 17, 1926, it had again contracted.

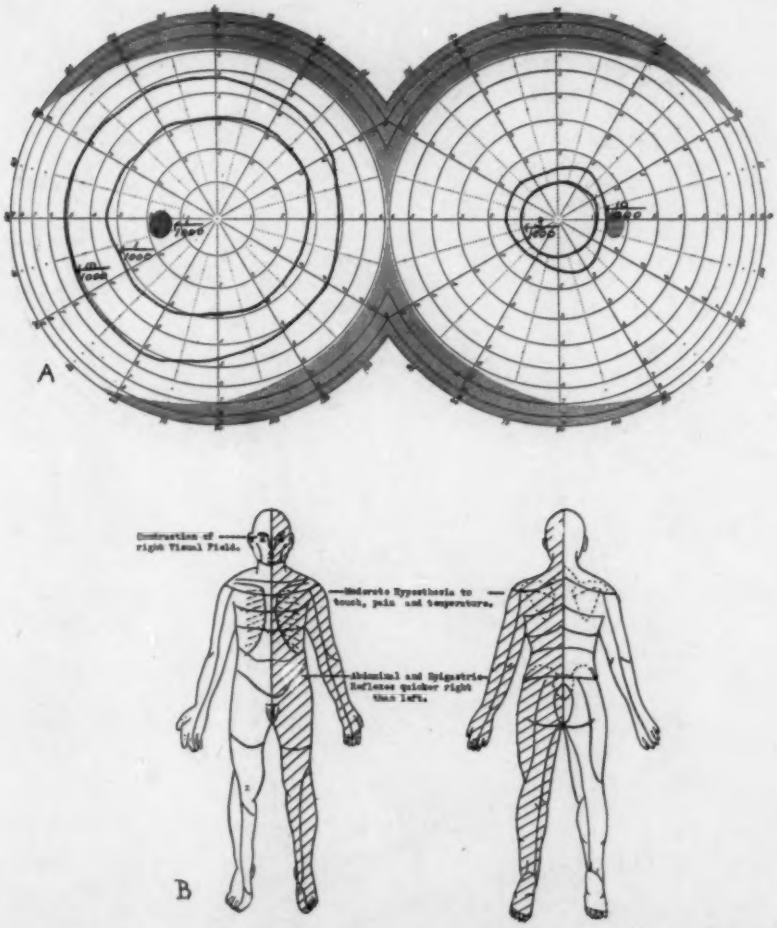
A
Contraction of right Visual Field.
Moderate Hypesthesia to touch, pain and temperature.
Abdominal and Epigastric Reflexes quicker right than left.
B

Fig. 32 (case 23).—*A*, hysterical contraction of the right visual field, present approximately nineteen months after head injury. In the left eye uncorrected vision was 20/40+; with the right eye the patient saw the card only. *B*, hysterical sensory changes coincidental with the contraction of the field. Both of these conditions improved when the patient was given a different occupation.

During the entire period of observation the pupils remained equal and reacted quickly to light and in accommodation. The extra-ocular movements were normal in all respects. On Aug. 28, 1924, complete bilateral anosmia was discovered. At times hypesthesia to touch, pain and temperature was described on the left side

(fig. 32); at other times the patient stated that he did not feel pin prick over any extremity or, in fact, over the body; on still other occasions the sensory picture appeared normal. No discrepancies of note were ever found in the reflexes. The mentality remained childish throughout the period of observation.

Impression.—The following conditions were considered to be present: compound, comminuted fracture of the left orbital region of the skull; severe

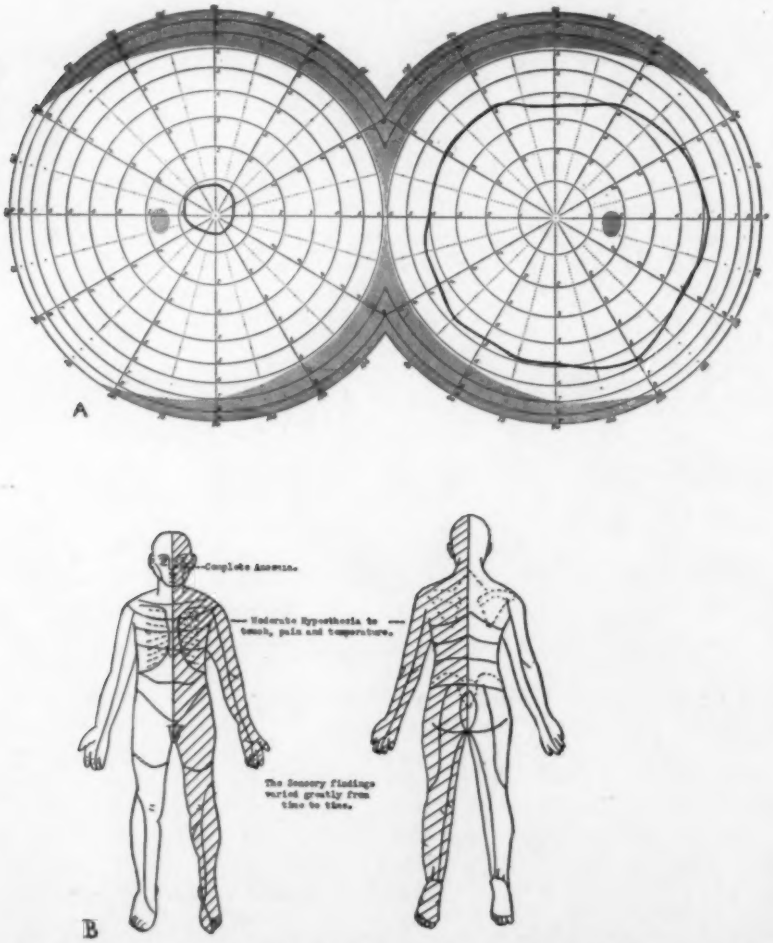

Fig. 33 (case 24).—*A,* Tubular vision in the left eye. (The representation of the visual field was transferred from the universal perimeter). Corrected vision was 20/200— in the left and 20/70— in the right eye. *B,* moderate hysterical sensory disturbance present thirteen months after a head injury. Marked improvement occurred nine years later.

concussion and contusion of the brain; primary atrophy of the left optic nerve of moderate degree; changes in the choroid; mental deterioration; manifestations of hysteria superimposed on the organic picture.

SUMMARY AND CONCLUSIONS

A brief résumé of the literature concerning traumatic lesions of the visual pathways is presented. Twenty-four cases in which various types of alterations in the fields followed craniocerebral injuries are reported.

An anteroposterior splitting of the chiasm apparently may result from a blow directed to the top of the head. Under such circumstances a contre-coup effect on the chiasm is brought about, even though the exact mechanism of its production is not clear.

INTERACTION OF BONE AND VARIOUS METALS

VANADIUM STEEL AND RUSTLESS STEELS

LAURENCE JONES, M.D.
AND
B. ALBERT LIEBERMAN JR., M.D.
KANSAS CITY, MO.

The interactions that occur between bone and metal are exceedingly complex. Almost without exception, past experiments have been limited to observation of the changes that occur in bone when the metallic foreign body is inserted in it. The problem cannot be solved from this point of view alone. The question does not involve merely the reaction of bone to metal but is concerned as much with the changes that occur in the metal when it is buried in bone.

A basic consideration is that the exact chemical composition of the metal tested must be known. Although this seems obvious, the omission of data on the composition of the metal from previous studies probably accounts for variations in the results. Only a few metals are relatively pure, the majority containing other substances in varying amounts; and alloys, or metal mixtures, which seem closely related may be chemically dissimilar. The inclusion of data on the composition of the metal in future experiments will go far toward insuring comparable statistics.

We recommend that the following postulates be adopted for studies of this nature: (1) The exact chemical composition of the metal used should be known rather than the generic name. (2) The reaction of the metal to bone should be studied as well as the reaction of bone to the metal.

Four alloys were chosen for investigation, one of vanadium steel and three of rustless steels of different composition. It will be necessary to explain briefly the reasons for the choice of these specific alloys. In December 1930 the American College of Surgeons requested the assistance of the United States Bureau of Standards in the establishment of a standard Lane plate. This committee met in November 1930, with Dr. Phillip D. Wilson acting as chairman. The other members consisted of several physicians interested in the subject and representatives of several manufacturers of these appliances. As the result of their deliberations a set of standards was adopted for the numerous Lane

From the Orthopedic and Surgical Services of the Menorah Hospital.

plates of the Sherman type.[1] They were to be made of a vanadium steel alloy known as Society of Automotive Engineers steel 6150, having the following composition:

Substance		Percentage
Carbon		0.45–0.550
Manganese		0.50–0.800
Chromium		0.80–1.100
Phosphorus	not over	0.040
Sulfur		0.045
Vanadium	not under	0.150
	desired	0.180

This alloy was recommended to Dr. Sherman by the engineers of the Carnegie Steel Company in Pittsburgh because it has great surface hardness. No physiologic tests were made.[2] It was thought that this would end two outstanding faults, the breakage of plates and the loosening of screws. Such has not been the case, and the reasons will be shown later.

Before 1924 rustless steel was not generally employed in bone surgery, but the work of Zierold gave an immediate stimulus to its extensive use.[3] A study was made of the reaction of bone to gold, silver, aluminum, zinc, lead, copper, nickel, high carbon steel and low carbon steel, stellite, copper-aluminum alloy, magnesium and iron. A finding of Zierold's and one which has not been given the recognition it deserves was that low carbon steels and high carbon steels produced extensive bone necrosis and were, in fact, the most irritant of any of the substances tested. This point is deserving of emphasis, as one still sees competent surgeons inserting carpenter's screws and nails in bone. Zierold's final conclusions were that aluminum, gold and stellite "tend to become encapsulated with but little hindrance to the reparative process. They are inert materials unaffected by the living cells and body cells." In reference to the reaction of bone to stellite, he concluded that it showed "the least departure from the normal. The type of reaction is similar and the degree is not outside the limits observed in the controls. In fact, it appears the metal merely occupies space affecting in no way the regeneration of bone and periosteum."

Recently the formula for this stellite was obtained. This is, approximately, "58 per cent cobalt, 35 per cent chromium and 4 per cent

1. Steel Bone Plates and Screws, United States Dept. Commerce, Bureau of Standards, Commercial Standard CS37-31.

2. Wilson, Phillip D.: Personal communication to the authors.

3. Zierold, A. A.: Reaction of Bone to Various Metals, Arch. Surg. **9**:365 (Sept.) 1924.

tungsten. The balance of the ingredients are iron, carbon and impurities."[4] In Zierold's work the terms "stellite" and "rustless steel" were used interchangeably. Inspection of the formula renders the term "rustless steel" for an alloy of this composition extremely questionable.

At the present time significant work is being done on this subject by Ménégaux, Moÿse and Odiette. They have found that there is no inhibition of growth in cultures of osteoblasts and fibroblasts when small disks of chrome-nickel steel alloys are added to them.[5] At the same time they found that gold, aluminum and lead have similar biologic action but cannot be recommended for osteosynthesis for physical reasons. The metals which they found to be nontoxic when tested by this method have the following European trade names: Duralumin, V_2A extra, Nicral D and Platino-stainless D. The formula for Duralumin is: copper, 4 per cent; magnesium, 0.5 per cent; manganese, 0.2 per cent, and silicon, from 0.3 to 0.5 per cent, the remainder consisting of aluminum. V_2A extra is made up as follows: chromium, 18 per cent, and nickel, 8 per cent, plus a small unspecified percentage of manganese and titanium. The formula for Nicral D is: chromium, 20 per cent, and nickel, 16 per cent. The formula for Platino-stainless D is: chromium, 18 per cent, and nickel 8 per cent, plus a small unspecified amount of tungsten. To quote directly, they "inhibit neither growth nor migration of osteoblasts or fibroblasts in vitro."

A large number of appliances for the internal fixation of bone made of rustless steel have been designed. The most outstanding example, of course, is the Smith-Petersen nail, but there are many others, including Steinmann pins and bone screws of special design.[6]

The term rustless steel requires definition. We did not know and we believe that the members of the medical profession generally do not recognize that the adjective "rustless" or "stainless" is applied to many alloys of dissimilar composition. They have this in common: They are all alloys containing from 7 per cent to much higher percentages of chromium and are low in carbon content. Nickel may be absent or may be present in a large quantity. In the presence of the higher percentages of nickel the amount of chromium is decreased.

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4. Haynes "Stellite" Company: Personal communication to the authors.

5. Ménégaux, G.; Moÿse, P., and Odiette, D.: Croissance des tissus conjonctifs et osseux cultivés "in vitro" en présence de certains métaux, Presse méd. **42**:658 (April 21) 1934.

6. Smith-Petersen, M. N.; Cave, E. F., and Vangorder, G. W.: Intracapsular Fractures of the Neck of the Femur, Arch. Surg. **23**:716 (Nov.) 1931. Jones, Laurence: Intracapsular Fractures of the Neck of the Femur, Ann. Surg. **97**:237 (Feb.) 1933. Henry, Myron O.: Intracapsular Fractures of Hip: New Device for Lateral Osteosynthesis, J. Bone & Joint Surg. **16**:168 (Jan.) 1934.

The original work on stainless steels was done by Brearley, Haynes, Cox, Hatch and Furness, and the generic term stainless steel was applied to the steel covered by their patents. These early steels contained chromium alone. The chrome-nickel steels were of a later vintage. Popular usage has caused all corrosion-resisting steels to be known as rustless steel, regardless of their chromium or nickel content.

From the almost innumerable varieties of rustless steels, three were chosen which are fairly representative of the group. The first is high in chromium content, with nickel entirely absent. It will henceforth be designated as nickel-free rustless steel. The approximate composition is as follows:

Substance	Percentage
Carbon	0.10, maximum
Manganese	0.30–0.60
Silicon	0.30–0.50
Phosphorus	0.03, maximum
Sulfur	0.30–0.45
Molybdenum	0.55 (approximate)
Chromium	14.00–15.50

The second alloy chosen is low in chomium content and high in nickel content, the proportion being about 1 : 3. It is termed high nickel rustless steel in this text. The approximate composition is as follows:

Substance	Percentage
Carbon	0.300– 0.50
Manganese	0.600– 0.90
Phosphorus	0.035
Sulfur	0.035
Silicon	1.250– 1.50
Copper	1.000– 1.50
Chromium	7.500– 9.00
Nickel	21.500–23.50

The third alloy tested is high in chromium content and low in nickel content, the proportion being about 2 : 1. For this reason it is called low nickel rustless steel. The approximate composition is as follows:

Substance	Percentage
Carbon	0.700, maximum
Manganese	0.400– 0.65
Phosphorus	0.035
Sulfur	0.035
Silicon	0.300– 0.75
Nickel	8.000– 9.50
Chromium	17.500-19.00

The physical properties of these three rustless steels vary. The alloy that is free from nickel is soft and easily machined. The two alloys containing nickel are very hard and become even harder during the process of cold-machining (austenitic property). Thus they require special tools for fabrication. For this reason any order addressed to a manufacturer for a prosthesis without specification of the exact formula of rustless steel desired will invariably be filled from the more easily machined nickel-free types. Investigation shows that practically all the appliances at present are made of rustless steels having approximately the first formula. In the light of the results that follow, this point should be remembered.

Through the courtesy of the chemical laboratories of the Vanadium Steel Corporation of America and the Crucible Steel Corporation of America, samples were furnished having the formulas just given. From these, tacks were accurately machined. The shape is adequately shown in figure 1. The measurements were: diameter of the head, 0.125 cm.; diameter of the shaft, 0.1 cm.; length of the shaft, 0.725 cm.

EXPERIMENTAL PROCEDURE

The experimental procedure in general consisted in weighing the tacks and then under aseptic precautions placing them in the bones of dogs. The reaction of the metal to the bone was studied by removing the tack, again weighing it and computing the loss of weight. The reaction of the bone to the metal was observed by fixing, sectioning and studying the defect in the bone created by the tack. Control holes were made for the purpose of studying the reaction of bone to a drill hole. Only large adult dogs were selected.

Dog 1.—This animal was a female police dog of mixed breed, about 1½ years old, weighing about 22 Kg. The central portions and the inside surfaces of both tibias in the midportions and the lateral surfaces of both femurs were exposed through incision. The periosteum was excised and retracted. A drill having a slightly smaller diameter than the shaft of the tack was used to perforate the cortex. The tacks selected were then lightly driven into this opening until the top of the head was flush with the periphery of the bone. In this experiment the tacks had the following locations: nickel-free rustless steel tack, right tibia; vanadium steel tack, left tibia; high nickeled rustless steel tack, right femur, and low nickel rustless steel tack, left femur. The periosteum and skin were closed in separate layers.

Dog 2.—This animal was a male dog of mixed breed, predominantly collie, about 2 years old, weighing about 24.5 Kg. In a manner exactly similar to that already described the tacks were placed in the following locations: low nickel rustless steel tack, right tibia; high nickel rustless steel tack, left tibia; nickel-free rustless steel tack, right femur; vanadium steel tack, left femur.

In these two experiments the tacks were allowed to remain in situ for thirty days, and the dogs were then killed.

Dog 3.—This animal was a large male "bull-police" dog, 3 years old, weighing 27 Kg.

The internal surfaces of both tibias were exposed for a distance of about 2½ inches (6.4 cm.), and four drill holes were made ½ inch (1.3 cm.) apart, in the longitudinal plane. The tacks on both sides from above downward were, in order of appearance: vanadium steel tack, nickel-free rustless steel tack, low nickel rustless steel tack and high nickel rustless steel tack. These were allowed to remain in place for forty days.

Fig. 1.—Roentgenograms of (*A*) both femurs and (*B*) both tibias of dog 1, taken thirty days after the insertion of the tacks. There is a marked periosteal reaction in the left tibia about a vanadium steel tack, with no demonstrable roentgenographic reaction about the other tacks.

Dogs 4 and 5.—The studies on these animals were started at the same time as the experiment on dog 3 and were performed in an exactly similar manner. Four tacks were placed in the central portions of both tibias of these dogs. At the time that dog 3 was killed certain phenomena of loss of weight of the metal were becoming apparent. It was deemed inadvisable to kill the dogs at this time, without the insertion of more samples.

Dog 4.—This animal was a female collie of mixed breed, aged 3 years, weighing 13.5 Kg. The tacks from above downward in the central portions of both tibias were, in order of appearance: vanadium steel tack, nickel-free rustless steel tack, low nickel rustless steel tack and high nickel rustless steel tack. At the end of the forty day period, which had marked the killing of the third dog, additional tacks were inserted in the following locations: two tacks of low nickel rustless steel in the lower external surface of the right and the left humerus, and two tacks of low nickel rustless steel just below the trochanters of both the right and the left femur. In the external surface of the lower ends of both femurs two vanadium steel tacks were placed. At the lower internal surface of each tibia, about 2 inches (5 cm.) below the other tacks already in situ, two tacks of high nickel rustless steel were inserted. At the end of an additional forty-five days the dogs were killed, and the tacks and the specimens of bone were obtained. Thus the eight tacks in the central portions of the tibias remained seventy-five days; all the others remained thirty days.

Dog 5.—This animal was a female halfbreed police dog, aged about 2 years, weighing about 23 Kg. The procedure of this experiment was similar to that of the foregoing in that at the first stage the central internal surfaces of both tibias were exposed and four tacks at ½ inch (1.3 cm.) distance from each other were inserted in the usual manner. On both sides the order from above downward was: vanadium steel tack, nickel-free rustless steel tack, low nickel rustless steel and high nickel rustless steel. At the end of thirty days additional tacks were placed in the following locations: vanadium steel tack, lower end of the right humerus; nickel-free rustless steel tack, lower end of the left humerus; high nickel rustless steel tack, just below the trochanter of the right femur; low nickel rustless steel tack, just below the trochanter of the left femur; low nickel rustless steel tack, external surface of the lower end of the right femur; vanadium steel tack, external surface of the lower end of the left femur; high nickel rustless steel tack, internal surface of the lower end of the right tibia, about 2 inches (3 cm.) below the tacks previously inserted, and nickel-free rustless steel tack in the same location on the left side. The time elements in the experiments on dogs 4 and 5 were exactly similar.

OBSERVATIONS

As certain of the metals caused considerable periosteal reaction, it was often quite a problem to remove the tacks without causing injury to them or to the specimens of bone. Certain minor variations in loss of weight are accounted for by this factor. For this reason a number of the tacks were selected with which there was no possibility of gross technical error in the computation of post-operative weight. Another reason for exclusion was the complete or partial extrusion from the bone.

Inspection of the tables show that the major portion of the loss of weight occurred within the first thirty days. It was also noted that the loss of weight was not affected by the close proximity of one tack to another or by the location of the tack in various bones.

Two sets of tacks, one of vanadium steel and the other of nickel-free rustless steel, when isolated from other tacks, were extracted from the bone without

TABLE 1.—*Loss of Weight of Vanadium Steel*

Pin	Dog	Bone	Weight of Tack, Gm. Before Insertion	Weight of Tack, Gm. After Removal	Percentage of Loss	Days in Bone	Comment
1	4	Tibia	0.242	0.221	8.60	75	Profuse hemorrhage from marrow
2*	4	Tibia	0.251	0.231	7.90	75	Extruded from bone
3*	3	Tibia	0.256	0.235	8.20	40	Heavy periosteal overgrowth
4*	3	Tibia	0.262	0.235	10.30	40	Tack injured in removal; heavy overgrowth of bone
5*	5	Tibia	0.262	0.241	10.20	75	Tack injured in removal; dense osteoperiosteal overgrowth
6	5	Tibia	0.264	0.244	7.60	75	Dense osteoperiosteal overgrowth
7	4	Femur	0.275	0.255	7.20	30	Slight periosteal overgrowth
8	4	Femur	0.278	0.254	8.60	30	Slight periosteal overgrowth
33	5	Humerus	0.200	0.181	9.50	30	Covered with soft loose periosteum
34	5	Femur	0.209	0.188	10.00	30	Slight periosteal overgrowth
36	2	Femur	0.231	0.210	9.09	30	Slight periosteal overgrowth
39	1	Tibia	0.297	0.277	6.56	30	Slight periosteal overgrowth

* Excluded from the final computation.

TABLE 2.—*Loss of Weight of Nickel-Free Rustless Steel*

Pin	Dog	Bone	Weight of Tack, Gm. Before Insertion	Weight of Tack, Gm. After Removal	Percentage of Loss	Days in Bone	Comment
9	4	Tibia	0.276	0.254	7.90	75	Slight periosteal reaction
10	4	Tibia	0.279	0.256	8.10	75	Periosteal overgrowth
11	3	Tibia	0.272	0.245	9.90	40	Osteoperiosteal overgrowth
12*	3	Tibia	0.269	0.245	8.90	40	Extruded from the bone
13	5	Tibia	0.275	0.254	7.60	75	Dense osteoperiosteal overgrowth
14	5	Tibia	0.280	0.274	1.90	75	Dense osteoperiosteal overgrowth
15*	4	Femur	0.285	0.265	7.00	30	Extruded from the bone
16	4	Femur	0.272	0.267	1.70	30	Slight periosteal reaction
40*	5	Tibia	0.221	0.220	0.67	30	Extruded from the bone
41	5	Humerus	0.241	0.230	4.70	30	Periosteal overgrowth
42	2	Femur	0.252	0.251	0.19	30	Slight periosteal reaction
45	1	Tibia	0.291	0.270	7.21	30	Slight periosteal reaction

* Excluded from the final computation.

TABLE 3.—*Loss of Weight of High Nickel Rustless Steel*

Pin	Dog	Bone	Weight of Tack, Gm. Before Insertion	Weight of Tack, Gm. After Removal	Percentage of Loss	Days in Bone	Comment
17*	4	Tibia	0.242	0.241	0.20	75	Extruded from the bone
18*	4	Tibia	0.245	0.238	2.80	75	Tack injured in removal; periosteal overgrowth
19	3	Tibia	0.249	0.245	1.60	40	Thin bony overgrowth
20	3	Tibia	0.251	0.246	2.18	40	Dense periosteal overgrowth
21	5	Tibia	0.256	0.255	0.39	75	Slight periosteal reaction
22	5	Tibia	0.257	0.254	1.30	75	Slight periosteal reaction
23	4	Humerus	0.259	0.254	1.70	30	Slight periosteal reaction
24	4	Humerus	0.260	0.260	0	30	Slight periosteal reaction
46*	5	Femur	0.220	0.216	1.80	30	Extruded from the bone
47*	5	Femur	0.228	0.228	0	30	Extruded from the bone
48*	2	Tibia	0.232	0.226	2.79	30	Tack injured in removal
52	1	Femur	0.238	0.234	1.88	30	Slight periosteal reaction

* Excluded from the final computation.

difficulty, whereas the tacks of high nickel rustless steel and and low nickel rustless steel were firmly held.

In addition to the fact that all the vanadium steel tacks were loose in the bone, an outstanding observation was the blackish discoloration of the tack hole and of the surrounding soft parts.

Loss of weight was high, as in the eight tacks listed in table 1. There was an average reduction of 8.38 per cent from the original mass.

In the case of nickel-free rustless steel, nine tacks were used, with an average loss of weight of 7.03 per cent (table 2).

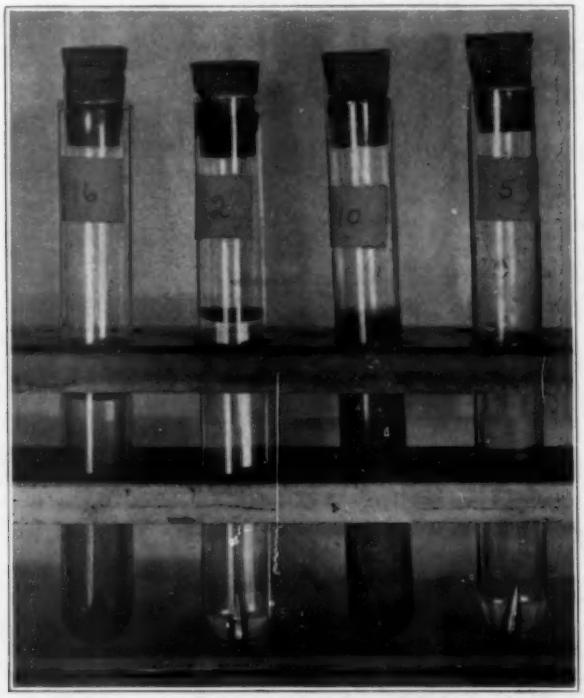

Fig. 2.—Test tubes containing, from left to right, a tack of nickel-free rustless steel, a tack of high nickel rustless steel, a tack of vanadium steel and a tack of low nickel rustless steel. There is complete absence of corrosion of both chrome-nickel rustless steels. The heavy precipitate in the first and third tubes illustrates the extensive corrosion of nickel-free rustless steel and vanadium steel by Ringer's solution.

The difference in loss of weight when the nickel-free rustless steel and the chrome-nickel alloys are compared is enormous. High nickel rustless steel had a loss of weight of 0.125 per cent in seven tacks, and low nickel rustless steel, a loss of weight of 0.8 per cent in nine tacks (tables 3 and 4).

The phenomenon of early and rapid loss of weight in two of the metals tested and of relatively little loss of weight in the others led to speculation as

to the cause. With the thought in mind that the corrosive effect of serum electrolytes might be a factor, four tacks of each metal were immersed in 5 cc. of Ringer's solution[7] for thirty days. The tubes were kept at 37.5 C. and gently

TABLE 4.—*Loss of Weight of Low Nickel Rustless Steel*

Pin	Dog	Bone	Weight of Tack, Gm. Before Insertion	Weight of Tack, Gm. After Removal	Percentage of Loss	Days in Bone	Comment
25	4	Tibia	0.313	0.313	0	75	Slight periosteal reaction
26	4	Tibia	0.313	0.310	0.95	75	Periosteal overgrowth
27	3	Tibia	0.311	0.307	1.10	40	Thin periosteal overgrowth
28	3	Tibia	0.307	0.304	0.81	40	Thin periosteal overgrowth
29	5	Tibia	0.300	0.297	1.00	75	Slight periosteal reaction
30	5	Tibia	0.295	0.291	1.30	75	Slight periosteal reaction
31*	4	Tibia	0.284	0.276	2.70	30	Slight periosteal reaction; partially extruded
32	4	Tibia	0.278	0.278	0	30	Periosteal overgrowth
53*	5	Femur	0.225	0.225	0	30	Extruded from the bone
54	5	Tibia	0.239	0.236	1.20	30	Slight periosteal reaction
55*	2	Tibia	0.274	0.268	2.07	30	Tack injured in removal
58	1	Femur	0.345	0.341	0.85	30	Periosteal overgrowth

* Excluded from the final computation.

TABLE 5.—*Loss of Weight in Ringer's Solution*

Pin	Weight of Tack, Gm. Before Insertion	Weight of Tack, Gm. After Removal	Percentage of Loss	Precipitate	Material
7	0.1902	0.1856	2.4	Heavy	Vanadium steel
8	0.1819	0.1761	3.2	Heavy	Vanadium steel
10	0.2037	0.1978	2.9	Heavy	Vanadium steel
11	0.2045	0.1990	2.7	Heavy	Vanadium steel
13	0.2487	0.2455	1.3	Heavy	Nickel-free rustless steel
14	0.2505	0.2479	1.1	Heavy	Nickel-free rustless steel
15	0.2442	0.2414	1.1	Heavy	Nickel-free rustless steel
16	0.2643	0.2618	0.9	Heavy	Nickel-free rustless steel
1	0.2239	0.2239	0	None	High nickel rustless steel
2	0.2447	0.2447	0	None	High nickel rustless steel
3	0.2264	0.2264	0	None	High nickel rustless steel
9	0.2244	0.2244	0	None	High nickel rustless steel
4	0.2821	0.2821	0	None	Low nickel rustless steel
5	0.2875	0.2875	0	None	Low nickel rustless steel
6	0.2625	0.2625	0	None	Low nickel rustless steel
12	0.3074	0.3074	0	None	Low nickel rustless steel

7. The formula used for Ringer's solution is as follows: Each 10 cc. contained 0.05 Gm. of sodium chloride, 0.002 Gm. of potassium chloride, and 0.004 Gm. of calcium chloride.

agitated once daily. The solution was changed every three days. That these electrolytes have a profound effect was clearly demonstrated as early as forty-eight hours after the beginning of this experiment. At the end of thirty days, corrosion was graphically illustrated by a heavy precipitate at the bottom of the test tubes. The changes in weight can be seen in table 5.

The reaction of the bone to the metal foreign body was studied. A thin segment of the bone containing the defect created by the tack was removed and fixed in a 10 per cent dilution of solution of formaldehyde U. S. P., and was then

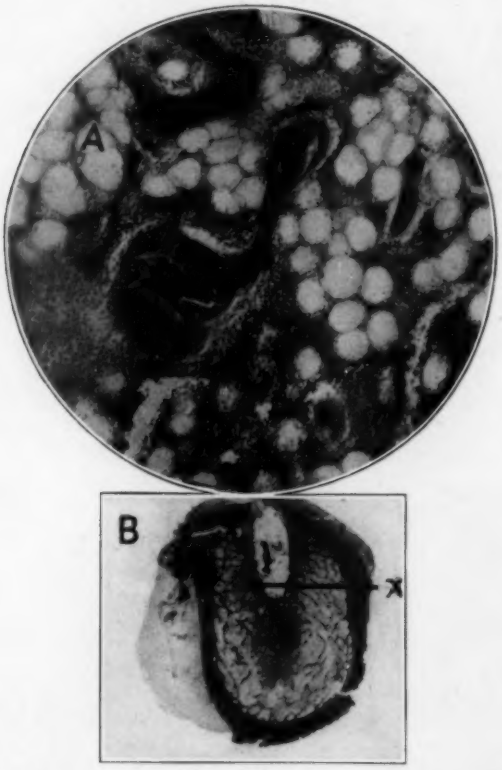

Fig. 3.—*A*, high power photomicrograph, showing reaction of bone to vanadium steel after the tack remained thirty days in the femur. *B*, low power photomicrograph, showing the extent of the zone of the medullary and periosteal reaction, *x* indicating the site shown in *A*. This demonstrates the extensive character of the inflammatory change and bone resorption induced by vanadium steel.

decalcified, sectioned and stained with eosin and hematoxylin. No blocks were selected for study from bones containing more than a single tack or from bones in which the tacks were left longer than thirty days. The intensity of the reaction varied considerably, even when the same metal was used. However, each metal had certain definite characteristics.

Macroscopically, the sections of vanadium steel showed a wide zone of increased density extending into the marrow for a distance approximately the length of the tack. Microscopically, there was marked fibrous thickening of periosteum, with recent inflammatory changes adjacent to the defect. The bone marrow showed a vastly increased cellular content around the wedge-shaped defect. The zone of reaction was double the width of the defect near the cortex, and at the apex of

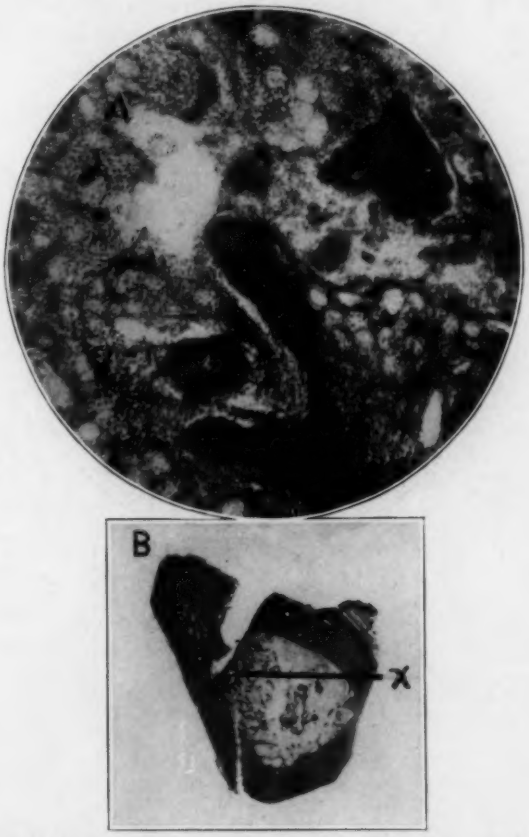

Fig. 4.—*A*, high power photomicrograph, showing reaction of bone to nickel-free rustless steel after the tack remained thirty days in the tibia. *B*, low power photomicrograph, showing defect created by the tack, and the extent of the zone of medullary reaction, *x* indicating the site shown in *A*. This demonstrates the resultant extensive hemorrhage, lymphocytic infiltration and necrosis of bone.

the wedge it extended almost to the opposite cortex. The cellular infiltrate was composed of lymphocytes and erythrocytes lying in greatly distended vessels or free in the marrow spaces. The erythrocytes predominated. The bone trabeculae proximal to the defect exhibited marked rarefaction by osteoclasis.

The gross reaction to nickel-free rustless steel varied from that to vanadium steel in degree only in that it was not quite as extensive. Microscopically, there were intense hyperemia and dense cellular infiltration of the bone marrow throughout the section. The prevailing cells were erythrocytes, with the lymphocytes represented in lesser number. Trabeculae lined the defect directly, and all those adjacent showed marked rarefaction by osteoclasis.

Grossly, the reaction to high nickel rustless steel presented a small zone of change. There was only slight periosteal overgrowth. Microscopically, the defect was lined by smooth bone surface or exposed trabeculae and bone marrow spaces

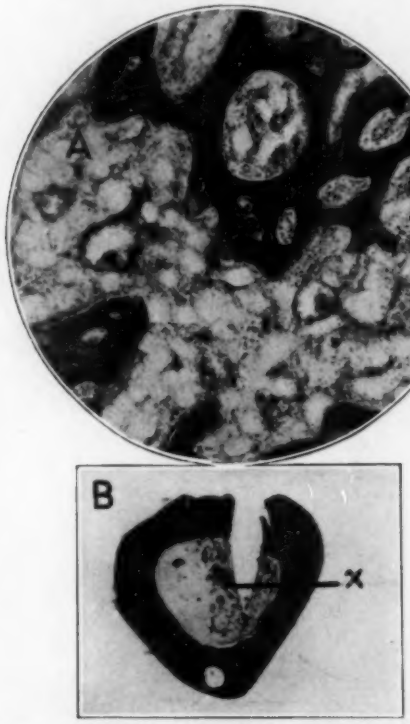

Fig. 5.—*A*, high power photomicrograph, showing reaction of bone to high nickel rustless steel after the tack remained thirty days in the tibia. *B*, low power photomicrograph, showing a narrowed zone of medullary reaction, *x* marking the site shown in *A*. Here is seen the greatly diminished inflammatory reaction, as compared with that seen in the two preceding figures. There are retention of trabecular structure and minimal resorption of bone.

without the formation of a definite fibrous tissue layer over considerable areas. There was moderate fibrosis in the medulla close to the margin. Hyperemia in this zone was marked, with scattered hemorrhages and cellular infiltration. The entire bone marrow in this section showed a similar condition. Osteoclasis was slight and was limited to the trabeculae adjacent to the defect.

Low nickel rustless steel showed a reaction but one of greatly diminished intensity when compared with that of the first two alloys described. The zone of reaction was extremely narrow. Microscopically, the defect was lined by a thick fibrous tissue layer which showed marked hyperemia. There was a small amount of hemorrhage accompanied by slight lymphocytic infiltration. The bony trabeculae immediately adjacent to the defect showed rarefaction by osteoclasis.

Fig. 6.—*A*, high power photomicrograph, showing reaction of bone to low nickel rustless steel after the tack remained thirty days in the tibia. *B*, low power photomicrograph, indicating almost complete absence of a fibrous capsule, *x* marking the site shown in *A*. This demonstrates a lesser amount of cellular reaction and generalized fibrous osteitis in medullary spaces, retention of trabecular structure and minimal destruction of bone.

The marrow throughout the entire section showed extensive fibrosis, some hyperemia with small hemorrhages and a scanty lymphocytic infiltration. The general picture resembled that of fibrous osteitis.

The reaction of this metal was observed in another section to show that there are slight variations in results even when the same metal is used. In this instance the defect was lined by a wide layer of fibrous tissue. The surrounding bone marrow showed extensive fibrosis accompanied by only slight hyperemia, and scattered hemorrhages. The remaining bone marrow was entirely free from changes. Only the bone trabeculae immediately adjacent to the peg hole showed slight osteoclasis.

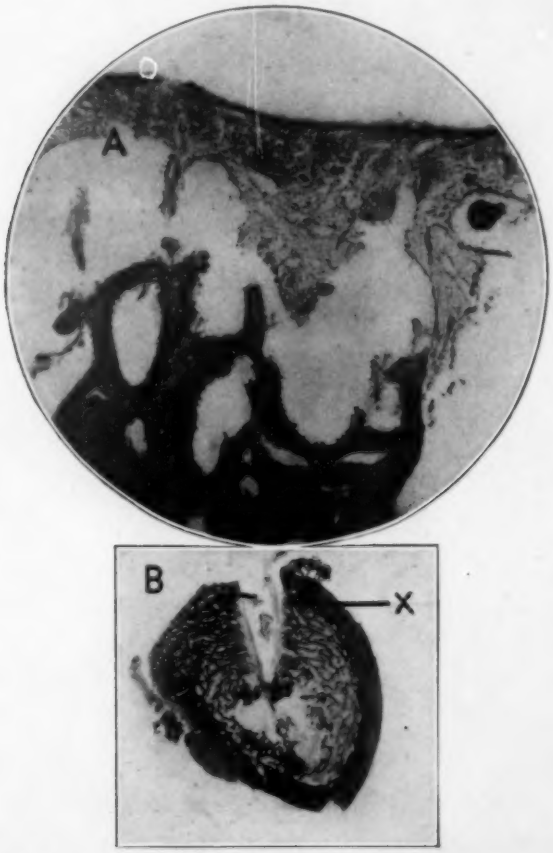

Fig. 7.—*A*, high power photomicrograph, showing reaction of bone to nickel-free rustless steel after the tack remained thirty days in the femur. *B*, low power photomicrograph, illustrating minor variations in the reaction, even when the same metal is used (see figure 6). Here there is the formation of a thin fibrous capsule, with almost complete absence of medullary reaction or fibrosing osteitis.

COMMENT

At the beginning of this article two postulates were proposed which we felt to be essential to any studies concerned with the interaction of bone and metal. The first of these original premises is confirmed, viz.,

that the exact chemical composition of any metal used for osteosynthesis should be known. This is true for two reasons, namely, that comparable experimental results by different observers demand this knowledge and that alloys of the same generic name may vary so widely in chemical composition as to give entirely dissimilar physiologic effects. The stellite or "rustless steel" used by Zierold was erroneously assumed to be a chrome or chrome-nickel alloy. The exact formula for a number of stellites was obtained only after prolonged investigation by the Haynes Stellite Compnay and after the conclusion of this experiment. Misapprehension as to the "rustless steel" used by Zierold has been shared generally, as the one in common use is an alloy of an entirely different composition and one that corrodes easily in bone. The original stellite used in his experiments is probably as nonirritant as the chrome-nickel alloys, as it resists corrosion in Ringer's solution quite as effectively.

The second postulate is that the reaction of metal to bone should be studied as well as the reaction of bone to metal. A metal should not be used for osteosynthesis which corrodes rapidly in body fluids. The simple test of first immersing it in Ringer's solution is one that should precede in vivo experiments or clinical use. It is significant and important clinically that the major portion of the loss of weight occurs early. It is during this period that fixation of bone becomes unstable. The joint effects of shrinkage of the prosthesis and of bone necrosis occur at the very period when firm support is most desired.

The portion of the experiment on the reaction of bone (third postulate) is incomplete. Undoubtedly, certain metals are relatively or completely nonirritant to the individual osteoblasts and fibroblasts. The opinion persists that the mass of a foreign body may be sufficient to interfere with the blood supply, causing reaction in varying degree. The experiment will be continued in an attempt to test the reaction of bone to objects of graded sizes.

It follows that all the mentioned factors are equally concerned in causing the complex set of phenomena which have been designated bone-metal interaction. The results of this experiment permit certain suppositions as to the train of events. Loss of weight of metal proceeds at a more rapid rate in bone than in Ringer's solution. This indicates that there is an additional factor which adds to the effect produced by the electrolytes contained in the tissue fluids. The accelerated rate of corrosion in vivo is probably due to the defensive reactions set up in the richly cellular bone marrow. With increasing corrosion and precipitation of irritant particles there is greater reaction of bone. The circle is finally broken with the formation of a fibrous tissue capsule and the complete encystment of the foreign body. The end-result is a corroded

and shrunken prosthesis lying loosely in an osseous defect made larger by necrosis of bone. Thus, the hypothesis is proposed that *the intensity of reaction of bone is directly proportional to the chemical changes that occur in the metal with which it is in contact.*

CONCLUSIONS

When a metal subject to corrosion is inserted into bone, a complex set of phenomena arise which has been termed bone-metal interaction. This experiment shows that the reaction of bone is linked with metallic corrosion.

Four metals were chosen for investigation, among them a specific alloy of vanadium steel prescribed for the standard Lane plate. Rapid corrosion and extensive necrosis of bone combine to contraindicate its use for osteosynthesis.

Nickel-free rustless steel, a metal widely used at present in bone prostheses, is placed in the same group. The same effects follow its use in only a slightly less degree.

The chrome-nickel rustless steels are the metals of choice. Corrosion of these alloys is minimal. Although they are not completely nonirritant in bone, their use is recommended.

TRUE HOUR-GLASS BLADDER

A CONSIDERATION OF ITS ETIOLOGY AND TREATMENT

J. S. EISENSTAEDT, M.D.
AND
T. G. McDOUGALL, M.D.
CHICAGO

The term hour-glass bladder has been used to designate a number of different pathologic and clinical entities. In this communication we shall not consider those cases included in Blum's [1] classification under type III, namely, the acquired variety due and subsequent to severe trauma, ulceration, operation, cicatricial contraction, tuberculosis or other inflammatory processes. We shall likewise not consider those cases of diverticula of the bladder erroneously reported as hour-glass bladder. The patient whom we have studied and operated on presented what Kretschmer and Morris [2] have called a true hour-glass bladder, regarding which there are but few reports in the literature. Young [3] described the condition as "one in which the bladder is circularly constricted and divided into two portions with a narrow canal of communication as in an hour-glass." He stated that he had operated on a patient in whom the circle of contracture passed across the posterior wall of the bladder at least 1 inch (2.5 cm.) behind the trigon. It is this type, in which the ureters enter the lower chamber of the bladder, which we are to describe and relating to which there are authentic reports by Fothergill,[4] Passow,[5] Müller,[6] Caulk,[7] Kretschmer and Morris [2] and Young.[3] Certain other reports do not state into which chamber the ureters entered and must therefore be excluded from this category.

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1. Blum, V.: Chirurgische Pathologie und Therapie der Harnblasendivertikel, ed. 2, Leipzig, Georg Thieme, 1929, p. 58.

2. Kretschmer, H. L., and Morris, H. L.: J. Urology **10**:181 (Aug.) 1923.

3. Young, Hugh, and Davis, D. M.: Young's Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 371.

4. Fothergill: Mem. Neurol. Soc. London, vol. 1, 1878, quoted by Caulk.[7]

5. Passow: De hypertrophia parietum vesicae urinae, Inaug. Dissert., Vratislaviae, 1848; quoted by Caulk.[7]

6. Müller, B.: Ein Fall von Missbildung am Beckenteil des weiblichen urogenital Apparates, Inaug. Dissert, Marburg, 1895.

7. Caulk, John R.: Ann. Surg. **71**:22 (Jan.) 1920.

Cases of true hour-glass bladder in which the ureters entered the upper chamber have been reported by Fuller,[8] Detweiler[9] and Cutter.[10]

This apparently rare anomaly has more than an academic interest for the urologist because of the need of an accurate diagnosis in certain cases of dysfunction of the bladder, as well as the necessity of rational surgical treatment when a diagnosis is made. The relationship between true hour-glass bladder and certain examples of transverse folds of the bladder must necessarily be explored, and we are fortunate in having two instances of transverse folds under observation at present. Zuckerkandl,[11] writing of transverse folds, said: "If they appear higher, that is, above the linea interureterica, and are raised to form sickle-like configurations and involve a greater portion of the periphery, they actually become a diaphragm resulting in hour-glass bladder."

ETIOLOGY

A careful survey of the few clinical reports available reveals almost total absence of reference to the etiology of this condition. In fact, discussion thereof in most communications is entirely omitted. Gruber[12] stated that certain types of hour-glass bladder occur as a result of excessive growth of tissue of mesodermal origin producing sickle-shaped horizontal folds. Delbet[13] said that the transversely bisected bladder indicates, in his opinion, the correctness of the modern point of view regarding the development of the bladder and that the contraction which occurs above the entrance of the ureters into the bladder is due to a local hypertrophy of the circular musculature of the bladder. Orth[14] designated the pathologic condition as a partial stricture of the middle portion of the bladder, and Pagenstecher[15] said that the condition which is most correctly termed "congenital hour-glass bladder occurs in cases in which anatomically and functionally different components meet or border on each other and results from the unequal growth of the normally separate bladder anlagen, which are noted in embryos 17 mm.

8. Fuller, E.: J. Cutan. & Genito-Urin. Dis. **18**:531 (Dec.) 1900.

9. Detweiler, E. L.: An Hour-Glass Bladder, Virginia M. Monthly **15**:644, 1888-1889.

10. Cutter: Lancet **1**:185, 1854.

11. Zuckerkandl, O., and von Frisch, A.: Handbuch der Urologie, Vienna, A. Hölder, 1903, vol. 2, p. 582.

12. Gruber, G. B., in von Lichtenberg, A.; Voelcker, F., and Wildbolz, H.: Handbuch der Urologie, Berlin, Julius Springer, 1928, p. 78.

13. Delbet, P.: Ann. d. mal. d. org. genito-urin. **25**:641, 1907.

14. Orth, Johannes: Lehrbuch der speciellen pathologischen Anatomie, Berlin, A. Hirschwald, 1889, vol. 2, p. 201.

15. Pagenstecher, E.: Arch. f. klin. Chir. **74**:186, 1904.

in length, namely, that of the corpus vesicae and that of the trigonum." Kaufmann [16] stated that the division of the bladder into two chambers is a very rare finding and that the explanation of this developmental defect is difficult. Aschoff [17] did no more than mention the anomaly.

Chwalla,[18] as a result of researches on a 37 mm. female embryo which he sectioned serially, found an interesting anomaly of the bladder, which was the only defect in the specimen. The bladder was markedly contracted. The mucosa about the ureteral orifices was arranged in folds. There was, in addition, a constriction of the lateral walls of the bladder. On sectioning the bladder, a membrane was found protruding into the cavity of the bladder, which was two or three cell layers thick and bound the anterior to the posterior wall. The membrane was thinner in the center and thicker toward the periphery. Similar to the constriction from side to side there was a moderate drawing in of the ventral wall of the bladder and a rather marked drawing in of the posterior wall. Chwalla interpreted this membrane as a persistent rest of the "ureter membrane," described by himself as a normal structure in embryos from 12 to 28 mm., which completely closes the openings of the ureters in embryos of this size but in embryos more than 28 mm. in length becomes dehiscent and disappears.

Paschkis and Krasa [19] had the opportunity of carefully studying the bladders of most of the animals from the zoological gardens in Vienna, and their monograph on the comparative anatomy of this organ is a classic. They found that in certain animals, especially in the monotreme, or duckbill, in the talpa, or mole, and in Equus asinus, a transversely divided bladder is the rule, and in a footnote they made the suggestion that this finding may have some bearing on the subject of transversely divided or hour-glass bladders seen in human beings.

We can obviously express no more than a theoretical opinion as to the cause of this rare anomaly based on what is at present known about the embryology of the bladder. First, we shall consider Krasa's and Paschkis' point of view, namely, that there exists a relationship between the divided bladders seen normally in certain lower animals and the very rare anomaly of hour-glass bladder in man. While the suggestion of an atavistic phenomenon is interesting and very plausible, it is a fact that in those animals which show the type of divided bladder noted

16. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, eds. 7 and 8, Berlin, W. de Gruyter & Co., 1922, p. 1116.

17. Aschoff, L.: Pathologische Anatomie, ed. 4, Jena, Gustav Fischer, 1919, vol. 2, p. 558.

18. Chwalla, R. O.: Zur Genese der angeborenen Sanduhrblase, Ztschr. f. urol. Chir. **23**:200, 1927.

19. Paschkis, R., and Krasa, F. C.: Ztschr. f. urol. Chir. **6**:1 (Jan.) 1921.

the musculature of the ureter most perfectly merges with the musculature of the bladder, and therefore a comparison based on this embryonic characteristic does not seem entirely warranted.

Fig. 1.—Cystogram taken in the oblique position. Note the diverticulum above the upper chamber of the hour-glass bladder.

Fig. 2.—Anteroposterior view of the bladder shown in figure 1. Note the incidental reflux up the right ureter.

In regard to Chwalla's [18] point of view, that the ledge or diaphragm may be a rest of the embryonic membrane of the ureter, it is to be said that, while it is conceded that Chwalla's description of the membrane closing the ureters in embryos of from 12 to 28 mm. is correct,

the conclusion based on a single finding of an anomaly in an embryo of 37 mm., that this defect is a rest of the membrane of the ureter, is not wholly tenable. It has not been shown that this membrane shifts or changes its position rather than merely becoming dehiscent and disappearing as is the rule. If the constricting band or perforated diaphragm were always noted exactly at the site of the entrance of the ureteral orifices, as in Mezan's case, rather than above them, as in our case and in others of similar character, or below their entrance into the bladder, as reported by Fuller, Detweiler and Cutter, more weight could be given to his opinion.

It seems that the opinion expressed by Pagenstecher and by Gruber is correct, namely, that an unequal growth of the anlagen of the bladder would account for both types of hour-glass bladder, whether the ureters entered into the upper or into the lower chamber. To support this view

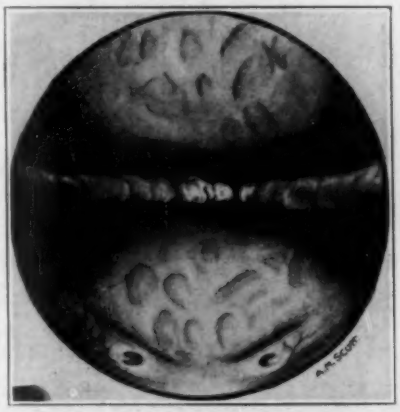

Fig. 3.—Diagrammatic drawing of cystoscopic findings. Note the heavy muscular ledge dividing the bladder cavity into two compartments.

it is to be recalled that the portion of the bladder between the ureteral orifices and the colliculus is of mesodermal origin, while the bladder cavity itself is of endodermal origin. The anlage of the ureter is gradually taken up by the anlage of the bladder, and any failure of perfect coalescence of these two structures of different origin could produce transverse folds or fibromuscular ledges either above or below the entrance of the ureters into the bladder.

PATHOLOGY

The pathology of true hour-glass bladder must be divided into a study of the separating membrane or diaphragm and of the pathologic physiology resulting from the anomaly. In none of the reports have we found any reference to the tissue removed at operation or to examination of the tissue post mortem. Our specimen was grossly a thick

muscular and fibrous structure varying from 1 to 1.75 cm. in thickness, completely crossing the posterior wall of the bladder and having its origin and insertion on the lateral walls well toward the ventral aspect of the bladder. In general it had the characteristics of tremendously hypertrophic bladder musculature which had undergone subsequent chronic inflammatory infiltration. Histologically, the picture was as follows: The section revealed an apparent increase of connective tissue throughout. In addition a few lymphocytic cells and endothelial cells were noted, some of which were perivascular in distribution. Sections

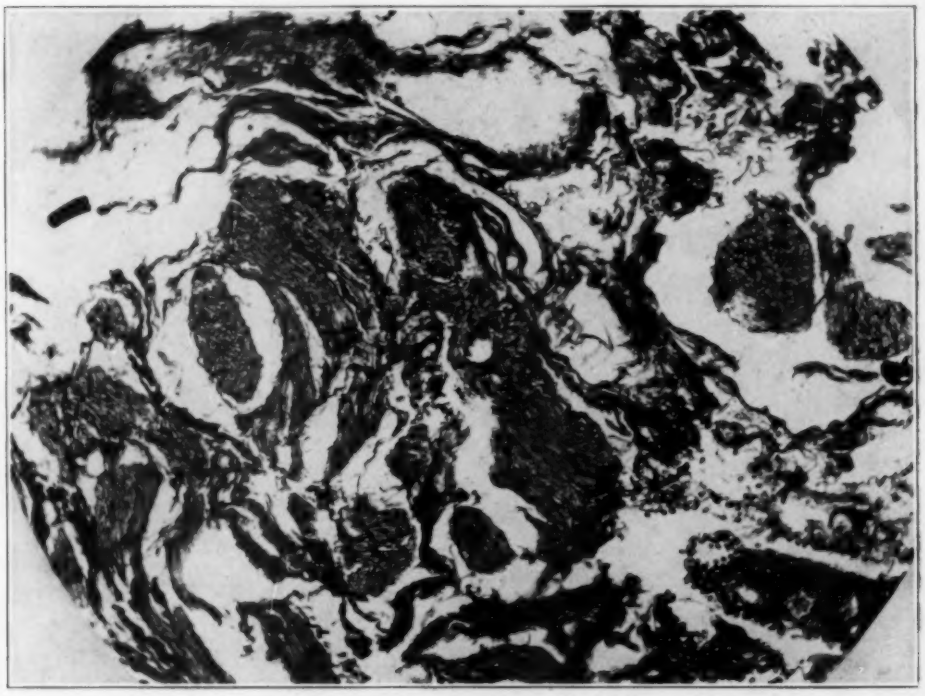

Fig. 4.—Histologic sections of the excised ledge. Note the hypertrophic muscular fibers.

which were stained according to the Van Gieson method also showed an increase of connective tissue. The muscle fibers and muscle bundles seemed somewhat larger than normal; otherwise no changes were noted.

PATHOLOGIC PHYSIOLOGY

The pathologic physiology of hour-glass bladder seems not too difficult of interpretation and depends largely on the character and contour of the constricting band. As a result of the presence of a prominent ledge or perforated diaphragm, the normal contractions of the detrusor muscle are inhibited from time to time, causing failure of the

upper chamber to empty itself completely. Owing to stasis in the upper chamber of the divided bladder, infection is invited at an earlier or later period in the patient's life. Bacteria, once having gained access to the bladder, persist indefinitely, as they do in bladders subjected to other obstructive processes.

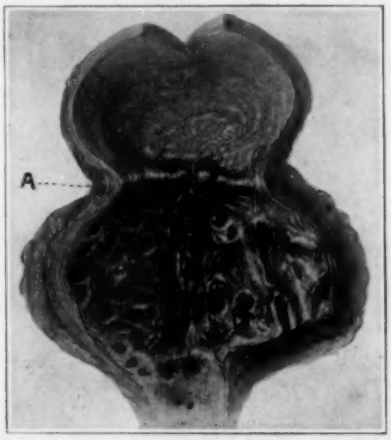

Fig. 5.—Drawing of the bladder in the case of Kretschmer and Morris [2] (courtesy of the Journal of Urology). *A* indicates the definite firm constriction which divides the bladder into two cavities.

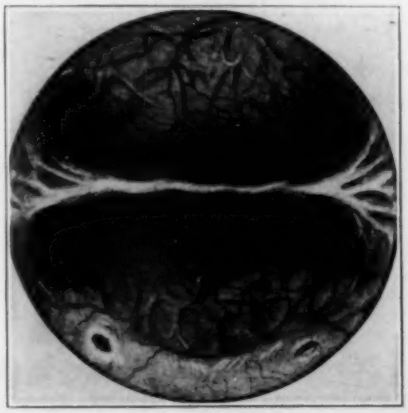

Fig. 6.—Drawing of the bladder in Caulk's [7] case (courtesy of the Annals of Surgery).

Vesical spasm, evidenced by frequent and painful urination, occurs, and the bladder as a whole or in part contracts more often on account of the irritability produced by inflammation. The increased mechanical work of the bladder musculature causes hypertrophy of its wall as a whole, more particularly in the immediate neighborhood of the con-

stricting band. Thus a vicious circle is produced, which, as the pathologic process advances, causes increased thickening of the band with subsequent narrowing and more marked retention in the proximal or upper chamber. Obviously, if infection remains absent till after middle life or if obstructive processes at or near the neck of the bladder do

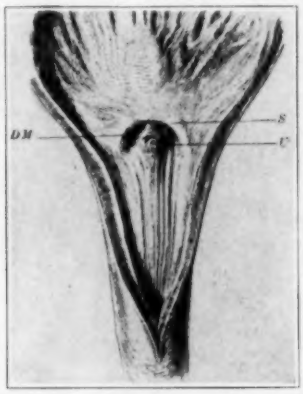

Fig. 7.—Bladder of female Echidna aculeata (courtesy of Paschkis and Krasa [19]). *DM* indicates the position of the ductus Mülleri, *S*, shows the sphincter, and *U*, the opening of the ureter.

Fig. 8.—Bladder of male Echidna aculeata (courtesy of Paschkis and Krasa [19]). *U* indicates the ureter, and *Dd*, the ductus deferens.

not occur, the hour-glass bladder of this type may function in a relatively normal manner.

The degree of development of the ledge or perforated diaphragm will determine the onset of conspicuous evidence of dysfunction. For example, if the communication between the two chambers is wide, retention in the upper chamber will be minimal, while if this communicating opening is narrow, the converse will be true. The condition tends to

become very slowly progressive but is rather promptly affected by any pathologic process involving the neighborhood of the neck of the bladder or structures distal to it, such as stricture of the urethra, prostato-vesiculitis, prostatic hypertrophy or contracture of the neck of the bladder.

SYMPTOMS

The symptoms of true hour-glass bladder are variable, and in no particular are they pathognomonic of the condition. In some cases

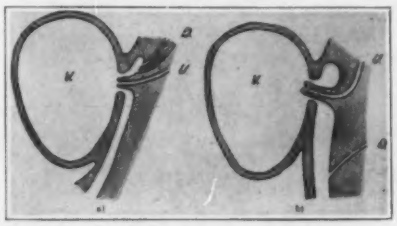

Fig. 9.—Sagittal view of bladder: (A) Echidna, (B) Didelphys (courtesy of Paschkis and Krasa [19]).

Fig. 10.—Anteroposterior view of the bladder fifteen months after operation.

urinary dysfunction had been present from childhood or early youth, as evidenced by enuresis and frequent and painful micturition. In other cases no symptoms of consequence evidenced themselves until middle age or later, when pathologic conditions having no connection with the congenital anomaly elicited symptoms of greater severity and degree than would have been occasioned by the pathologic process present, if uncomplicated. Pagenstecher remarked that clinical symptoms usually appear first when the constriction becomes so marked that the emptying of the upper chamber is greatly interfered with. Our patient presented the characteristics noted and undoubtedly had an exaggeration of the comparatively mild symptoms of his childhood and youth as a result

of the interference with urinary outflow. The presence of changes in the neighborhood of the neck of the bladder unquestionably had considerable bearing on the inflammatory as well as on the mechanical pathologic elements in the clinical picture, as observed before operation.

REPORT OF A CASE

Present Complaint.—O. B., aged 42, was admitted to the hospital because of urinary frequency, dysuria, nocturia (he arose five or six times a night) and pain in the region of the bladder.

History.—The patient stated that he suffered from enuresis until he was 14 years of age, at which time this condition ceased. No other illnesses of consequence were mentioned in the anamnesis. He said that he had not had venereal

Fig. 11.—Lateral view of the bladder shown in figure 10, fifteen months after operation.

disease. In 1918 he had influenzal pneumonia. During his convalescence he noticed some dysuria, which had gradually become worse until the time of admission. He stated that the dysuria became aggravated when he "caught cold." In 1925 the dysuria, frequency and pain in the region of the bladder were so severe that he was required to undergo a cystoscopic examination, which was done elsewhere. After cystoscopy he had complete retention of urine owing to the presence of blood clots in the bladder. A cystotomy was then done; an inlying urethral catheter was tied in, and the opening was permitted to close after five weeks. The symptoms continued the same, and he went to a clinic in the Northwest, where a diagnosis of moderate pyelitis, chronic prostatitis and posterior urethritis was made.

Physical Examination.—The results of general external examination were negative except for definite and marked suprapubic tenderness. The results of the various examinations were as follows:

Rectal Examination: Rectal examination revealed a prostate gland which was slightly enlarged, unevenly indurated and markedly tender. There were a moderate number of pus cells in the expressed fluid. The seminal vesicles were palpable, soft and very sensitive. The urine on repeated examination showed many pus cells and red blood cells.

Cystoscopic Examination: A no. 21 Brown-Buerger cystoscope passed with slight difficulty. The contents of the bladder were turbid. The bladder vault was moderately hyperemic. An opening of a small diverticulum at the dome was visualized. The trigonum was edematous and reddened. Both ureteral orifices were slitlike and contracted rhythmically. What appeared at first to be the opening of a diverticulum was noted about 1½ inches (3.7 cm.) above the upper margin of the trigon. This was shown later to be a transverse ledge extending across the posterior and lateral walls of the bladder, having its origin and insertion well toward the ventral wall of the viscus. The ledge was thick and appeared as a markedly hypertrophic musculature. A no. 6 catheter failed to pass up the ureter on either side at the first attempt but was eventually passed after no. 5 bougies had previously been passed on both sides. Cultures of the urine from the pelvis of the right kidney yielded streptococci. The pyelograms showed no abnormality other than a slight blunting of the calices of the right kidney.

Urethroscopic Examination: Urethroscopic examination revealed an enlarged verumontanum with prominent sulci on each side. On the left side was an opening into a pocket or sac which undermined the trigon for about 2 cm. The opening was slightly irregular, and at the time of examination it was impossible to state whether the pocket seen might have resulted from trauma at the time of cystoscopy in 1925 or whether it was a congenital anomaly.

Cystogram: The cystogram, especially in the lateral view, showed an hourglass outline. The upper chamber was somewhat larger than the lower chamber. There was a marked indrawing of the ventral as well as of the dorsal wall of the bladder. A similar constriction was noted from side to side in the cystogram made from an anteroposterior view. The anterior wall was irregular in outline, and on the posterior wall above the constriction there were several small cellules. At the dome a moderate-sized diverticulum was noted.

Operation.—With the patient under spinal anesthesia, after excision of the scar in the skin left by the cystotomy, the bladder was exposed in the usual manner. The peritoneal fold was detached by dissection with the fingers, with slight difficulty, up to the vertex, and the urachus was severed. The small diverticulum at the dome was resected extravesically, and repair of the defect was made in the usual manner. On exploring the interior of the open bladder, the wall of which was very markedly thickened, especially above the partial diaphragm noted on cystoscopic examination, the constricting band was seen and was found to be from 1 to 1.75 cm. in thickness. The greatest thickness was at its junction with the wall of the bladder. It appeared as a somewhat irregular band of hypertrophic muscle fibers. It was seen to divide the bladder into two chambers with a communicating opening, which would approximately admit the tips of three fingers. The entire muscular band was excised and the defect was sutured. The bladder was closed about a Pezzar catheter, which was left in the upper angle of the opening made by cystotomy.

Operation for Resection of the Neck of the Bladder.—Approximately three months after the removal of the constricting ledge, the Pezzar catheter having been left in place, the bladder was again opened, and with the electric cutting

current a large V-shaped wedge was removed from the lower half and the neck. After two weeks the Pezzar catheter was removed, and the bladder was permitted to close.

The patient was able to urinate readily, and there was no residual urine. Cystograms taken twelve months after the resection of the neck of the bladder showed a remarkable change, and the appearance closely approached the normal outline of the bladder both in the anteroposterior view and in the lateral or oblique position.

COMMENT

Diagnosis.—The direct diagnosis of true hour-glass bladder is best made by cystoscopy and by stereoscopic cystography. The absence of any pathognomonic subjective symptoms, except the notable symptom of prolonged urinary dysfunction in childhood and adolescence, make the clinical history of less value than usual.

Differential Diagnosis.—In the diagnosis of this rare type of anomaly it must be differentiated from all other processes obstructive to urination. One must consider prostatic hypertrophy, hypertrophy of the interureteral ridge, neurogenic changes in the bladder, diverticulum and, from the cystographic aspect, urachal cysts and diverticula.

Treatment.—The treatment should be directed toward relief of any obstruction at the neck of the bladder, and from our experience in this one case, we believe that resection of the diaphragm or ledge is indicated. Our patient at the time of writing has no residual urine.

SUMMARY AND CONCLUSIONS

A case of true hour-glass bladder is reported, probably the sixth or seventh of this type (Blum's type II) in the literature.

Considerations of its etiology are discussed, and they coincided entirely with the views of Pagenstecher and Gruber.

While it is impossible to contradict categorically the theoretical considerations advanced by Krasa and Paschkis and by Chwalla, we are inclined to the opinion that their hypotheses are too sharply defined in the light of the present incomplete understanding of the pathogenesis of this anomaly.

Surgical treatment is to be directed toward any obstruction at the neck of the bladder, and resection of the constricting band appears to be indicated.

A remarkable return toward normal function and normal outline of the bladder is evidenced by cystograms made a year after resection of the neck.

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RELATIONSHIP OF GASTRIC ACIDITY TO PEPTIC ULCERATION

I. EFFECT OF HYDROCHLORIC ACID, OF HISTAMINE AND OF DEVIATION OF BILE

MIMS GAGE, M.D.

ALTON OCHSNER, M.D.
AND
KIYOSHI HOSOI, M.D.
NEW ORLEANS

The relationship of gastric acidity to peptic ulceration has been debated for years. Volumes have been written, supported by clinical, statistical and experimental data, on the subject of the primary etiologic factors in the genesis of peptic ulceration. From the present knowledge, it is safe to assume that no one factor can be held responsible for ulcer in general. Several factors are usually operative in the causation and prolongation of the ulcerous condition; or, according to Tendeloo,[1] there is a constellation of factors. Indeed, Alvarez[2] reminded his readers that there may be several types of the disease in different parts of the world. It is this very complexity of causes that has been the incentive of much experimentation. The present tendency is to consider peptic ulceration as a local manifestation of systemic disease or of disease elsewhere in the body rather than as an involvement sui generis of the stomach or duodenum. The nature of the local manifestation, however, has given rise to much discussion. It cannot be denied that purely local causes, such as direct violence and corrosive poisons, may produce acute ulcers. Excellent reviews on the pathogenesis of peptic ulcer have been made by Hurst,[3] Halperin,[4] Smithies,[5] Held and Goldbloom,[6] Raine[7] and Carnot and Gaehlinger.[8] Clinically, we have come to the conclusion that whereas there are many important factors responsible for the causation and persistence of peptic ulcer, the three most important are: (1) the inherent predisposition to formation of ulcer,

From the Department of Surgery, Tulane University School of Medicine.

1. Tendeloo, N. P.: Berl. klin. Wchnschr. **58**:1, 1921.
2. Alvarez, W. C.: Am. J. Surg. **18**:207, 1932.
3. Hurst, A. F.: Guy's Hosp. Rep. **74**:413, 1924.
4. Halperin, G.: Internat. Abstr. Surg. **43**:173, 1926.
5. Smithies, F.: Ann. Clin. Med. **4**:468, 1925.
6. Held, I. W., and Goldbloom, A. A.: M. Clin. North America **1**:319, 1930.
7. Raine, F.: Wisconsin M. J. **30**:540, 1931.
8. Carnot, P., and Gaehlinger, H.: Paris méd. **1**:309, 1931.

i. e., ulcer diathesis; (2) susceptibility of the tissue and (3) increased gastric acidity. If this conception of the problem is correct, the clinician's therapeutic endeavors should be directed toward controlling the gastric secretion and acidity, because there is probably little that can be done to change the inherent predisposition and susceptibility of the tissue.

The acidity of freshly secreted pure gastric juice is at about the level of 0.5 per cent hydrochloric acid, which is rapidly reduced to that of 0.15 per cent hydrochloric acid during digestion. This self-regulation of the acidity of the contents of the stomach is effected through the following factors (Bennett,[9] Babkin [10]): (1) saliva and food materials, (2) gastric mucus, (3) regurgitated duodenal contents, (4) variations in the acidity of the gastric juice and (5) the water and chloride content of the body. Abundant clinical and experimental evidence is now at hand to show that there is a reflux of bile and pancreatic juices into the stomach (Moppert,[11] Apperly,[12] Medes and Wright [13]). Iwanow [14] and Wright and Medes [15] noted at times a marked dissociation of the regurgitation of bile and of pancreatic juice.

Numerous experiments have been devised to study the protective influence of the alkaline duodenal contents in the prevention of peptic ulceration. The underlying principle of all the different methods is the same, whether duodenal contents are deviated in toto or separately as bile, pancreatic juice or succus entericus. The experiments of Patrie,[16] Mann [17] and others have shown how technically simple it is to anastomose the pancreatic or bile ducts into other hollow viscera. Mann and Williamson [18] in this country and Weiss and his associates [19] in France have done much to popularize the method of "duodenal drainage." The entire duodenal contents have been deviated by the various methods of duodenectomy, with loss of both the bile and the pancreatic juice,

9. Bennett, T. I.: Guy's Hosp. Rep. **71**:286, 1921.

10. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin. Julius Springer, 1914; Canad. M. A. J. **17**:36, 1927.

11. Moppert, G. G.: Presse méd. **29**:415, 1921.

12. Apperly, F. L.: M. J. Australia **1**:33, 1923.

13. Medes, G., and Wright, C. B.: J. Clin. Investigation **6**:403, 1928.

14. Iwanow, W.: Arch. f. Verdauungskr. **38**:223, 1926.

15. Wright, C. B., and Medes, G.: Proc. Soc. Exper. Biol. & Med. **24**:904, 1927.

16. Patrie, H. H.; Pyle, L. A., and Vale, C. F.: Surg., Gynec. & Obst. **24**: 479, 1917.

17. Mann, F. C., and Kawamura, K.: An Experimental Study of the Effects of Duodenectomy, J. A. M. A. **73**:878 (Sept. 20) 1919.

18. Mann, F. C., and Williamson, C. S.: Ann. Surg. **77**:409, 1923.

19. Weiss, A. G., and Gurriaran, G.: Compt. rend. Soc. de biol. **102**:48, 1929; Arch. d. mal. de l'app. digestif **20**:63, 1930.

to the outside, or by the method of duodenal drainage, with conservation of these juices, into the lower portion of the small intestine (Steinberg;[20] Mann[21]), appendix (Winkelbauer and Hogenauer[22]), cecum, rectum (Leriche[23]), pelvis of the kidney (Kapsinow[24]) or urinary bladder (Leriche and his associates[25]). In these operations for the establishment of duodenal drainage the line of deviation is made in the proximal portion of the duodenum itself (Langenskiöld[26]), at the pyloric sphincter (Mann and Williamson) or in the pylorus (Morton;[27] McCann;[28] Exalto;[29] Winkelbauer and Hogenauer). Of course, in all, the continuity of the gastro-intestinal tract is reestablished. A survey of the enormous literature on operations for the establishment of duodenal drainage and of the results obtained by these careful investigators shows that there is indeed a great variation from Ivy's[30] 5 per cent to Morton's[27] 100 per cent incidence of jejunal ulcer following duodenal drainage. Mann[21] and Owings and Smith,[31] after obtaining typical chronic jejunal ulcers by duodenal drainage, secured healing of these ulcers by reconducting the duodenal contents over the ulcerated areas. Even an ulcer which had perforated the entire thickness of the jejunal wall would almost entirely disappear within twenty-five days after it was protected from the gastric contents. When the alkaline digestive juices were again short-circuited, the ulcer reformed. Mann maintained that although the great importance of chemical factors is recognized, the mechanical factors involved in the production of ulcer are not suffi-

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20. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in the Chemistry of the Stomach Following Gastric Operations, Arch. Surg. **15**:749 (Nov.) 1927.

21. Mann, F. C.: S. Clin. North America **5**:753, 1925; Tr. A. Am. Physicians **42**:224, 1927; Am. J. Surg. **7**:453, 1929.

22. Winkelbauer, A., and Hogenauer, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:49, 1928.

23. Leriche, R.: J. de chir. **38**:465, 1931.

24. Kapsinow, R.: Ann. Surg. **83**:614, 1926.

25. Leriche, R.; Fontaine, R., and Hermann, L.: Compt. rend. Soc. de biol. **107**:1025, 1931.

26. Langenskiöld, F.: Scandinav. Arch. f. Physiol. **31**:1, 1914.

27. Morton, C. B.: Ann. Surg. **85**:207 and 879, 1927; **87**:401, 1928; Am. J. M. Sc. **177**:65, 1929.

28. McCann, J. C. : Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Nov.) 1929.

29. Exalto, J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

30. Ivy, A. C.: Am. J. Physiol. **49**:143, 1919; Contributions to the Physiology of the Stomach: II. Studies in Gastric Ulcer, Arch. Int. Med. **25**: (Jan.) 1920; Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540 (Dec. 4) 1920; Nebraska M. J. **14**:137, 1929.

31. Owings, J. C., and Smith, I. H.: Proc. Soc. Exper. Biol. & Med. **29**:832, 1932.

ciently appreciated. A jejunal ulcer develops at the site of greatest impingement by the acid gastric contents—lateral and posterior to the central axis of the intestine. Mann and Bollman [32] concluded that in the prevention of peptic ulcer duodenal mucosa and secretion are probably the most important factors, bile is of least importance and pancreatic secretion is intermediate between the two. On the other hand, Graves [33] and DeBakey,[34] working in the experimental laboratory at Tulane University, observed that bile was probably the most important alkaline secretion in the prevention of peptic ulceration, that duodenal secretions (succus entericus) were least important and that pancreatic juice occupied an intermediate position. From the experiments recorded in the literature on total or isolated deviation of the alkaline duodenal contents, the following conclusions are indicated: The sensitivity of the intestinal mucosa to ulceration increases progressively from the duodenum to the ileum. Total deviation of the alkaline duodenal contents is more effective in producing ulceration than the isolated deviation of duodenal, biliary or pancreatic secretions. The question of experimental reflux of the entire duodenal contents into the stomach in the prevention of peptic ulceration is a subject still sub judice, although there is much evidence to show that this can prevent peptic ulceration or, if an ulcer is already present, promote its healing.

Artificial hyperacidity produced experimentally by the feeding of hydrochloric acid (Bolton;[35] Langenskiöld; Mann and Bollman; Friedenwald, Feldman and Morrison [36]) results in the formation of erosions and ulcerations, but it does not prevent their healing, except when highly corrosive concentrations are used. Obviously such high concentrations are not found in the human stomach, even in one which is the seat of peptic ulceration. Instead of feeding hydrochloric acid one can stimulate gastric secretion in laboratory animals and in man by the subcutaneous, intramuscular or intravenous injection of histamine (Popielski;[37] Best and McHenry [38]). Hence it is natural that histamine should be used to produce peptic ulcer experimentally by its stimulating effect on the

32. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers, J. A. M. A. **99**:1576 (Nov. 5) 1932.

33. Graves, A. M.: Combined and Separate Effects of Bile, Pancreatic Secretion and Trauma in Experimental Peptic Ulcer, Arch. Surg. **30**:833 (May) 1935.

34. DeBakey, M.: Peptic Ulceration, Arch. Surg., to be published.

35. Bolton, C.: Lancet **1**:1330, 1908; J. Path. & Bact. **14**:418, 1909; **20**:133, 1915.

36. Friedenwald, J.; Feldman, M., and Morrison, S.: J. Exper. Med. **57**: 203, 1933.

37. Popielski, L.: Arch. f. d. ges. Physiol. **177**:214 and 237, 1919.

38. Best, C. H., and McHenry, E. W.: Physiol. Rev. **11**:371, 1931; J. Physiol. **70**:349, 1930.

acid-secreting cells of the stomach during fasting. It has been so used in the rat (Büchner [39] and Molloy [40] and Siebert; [41] Bürkle-de la Camp [42]), in the mouse (Harde [43]), in the cat (McIlroy; [44] O'Shaughnessy [45]), in the rabbit (Matsueda [46]), in the guinea-pig (Harde; Matsueda) and in the dog (Matsueda; Puhl and Brodersen; [47] Friedenwald, Feldman and Morrison). The gastric juice secreted as a result of adequate doses of histamine is capable of producing peptic injury in the mucosa of the stomach, showing all transitions of mucosal changes from erosion to acute and chronic ulcers, this depending on whether or not the animal is fasting.

Since Meckel [48] first described his diverticulum in 1815, more and more interest is being shown in this condition because of the dramatic clinical picture of ulceration, hemorrhage and perforation which the functionally active dystopic gastric mucosa when present in Meckel's diverticulum is wont to produce through its acid peptic secretion. These ectopic tissues, the heteromorphoses of the biologists and the heteroplasias of the pathologists, have long held the keen attention of investigators, as judged from the extensive literature on the subject (Nicholson; [49] Taylor [50]). All these congenital heterotopias, whether of the gastric gland or of the intestinal gland type, are explainable perhaps by the ontogenetic history of the patient; they are the expression of his dysontogenesis. Such congenital heterotopias of various types occur in different portions of the gastro-intestinal tract. Recently, Mondor and Lamy [51] collected reports of nearly one hundred cases of ulcer of Meckel's diverticulum. A similar condition exists after the performance of a gastro-enterostomy, when jejunal mucosa becomes bathed with the acid secretions of the stomach, ulceration often resulting. When an isolated loop of small intestine is used to form a fistulous

39. Büchner, F., and Knötzke, F.: Beitr. z. path. Anat. u. z. allg. Path. **80**: 496, 1928.

40. Büchner, F., and Molloy, P. J.: Klin. Wchnschr. **6**:2193, 1927.

41. Büchner, F.; Siebert, P., and Molloy, P. J.: Beitr. z. path. Anat. u. z. allg. Path. **81**:391, 1928.

42. Bürkle-de la Camp, H.: Deutsche Ztschr. f. Chir. **220**:31, 1929.

43. Harde, E.: Compt. rend. Soc. de biol. **109**:1326, 1932.

44. McIlroy, P. T.: Proc. Soc. Exper. Biol. & Med. **25**:268, 1927.

45. O'Shaughnessy, L.: Lancet **1**:177, 1931.

46. Matsueda, A.: Klin. Wchnschr. **10**:2265, 1931.

47. Puhl, H., and Brodersen, H.: Arch. f. klin. Chir. **168**:31, 1931.

48. Meckel, J. F.: Arch. f. d. ges. Physiol. **1**:293, 1815.

49. Nicholson, G. W.: Guy's Hosp. Rep. **71**:222, 1921; **72**:193, 333 and 402, 1922; **73**:37, 164 and 298, 1923; **74**:81, 1924.

50. Taylor, A. L.: J. Path. & Bact. **30**:415, 1927.

51. Mondor, H., and Lamy, M.: J. de chir. **41**:553, 1933.

tract for the stomach (Goldberg;[52] Harper[53]), a chronic peptic ulcer develops in the mucosa of this fistula, just distal to the suture line between it and the stomach. Matthews and Dragstedt[54] reproduced Meckel's diverticulum with heterotopia by making a small Pavlov pouch which emptied into the isolated loop of the lower portion of the ileum. When the gastric pouch, with or without nerves, was implanted into the ileum, the incidence of ulcer was 100 per cent, but it was only 85 per cent when the pouch was implanted into the jejunum.

PROCEDURE

The present investigation[55] was undertaken in an attempt to evaluate the etiologic importance of gastric acidity. The effects of increased gastric acidity obtained by feeding hydrochloric acid and by stimulation with histamine were determined. Subsequently the incidence of peptic ulceration was determined in animals in which gastric pouches from the greater and lesser curvatures of the stomach, respectively, were anastomosed with the jejunum. Normal healthy dogs were used in all experiments. Every animal was weighed. The range of normal gastric acidity (free, combined and total) was first determined from two to five different times at intervals of from four or five days to a week following a standard test meal consisting of 22 Gm. of cracker meal in 250 cc. of water given through a stomach tube after fasting. When the following series of experiments was started the animals fasted on alternate days, at which time either the feeding of hydrochloric acid or injections of histamine were given and gastric analysis was carried out. Histamine acid phosphate was used. The solution was prepared by weighing the chemical under sterile conditions and dissolving it in sterile distilled water. In none of the animals did an abscess develop at the site of the injections. For the determination of gastric acidity, the technic as described in Bass and Johns' "Practical Clinical Laboratory Diagnosis"[56] was followed, di-methylamino-azobenzene and phenolphthalein being used as indicators. Computation gave values for free hydrochloric acid and total acidity. The difference between them represented the value for combined hydrochloric acid. The presence of bile and mucus was noted in each specimen obtained through the stomach tube.

A total of 125 dogs was used, but of this number 69 died at various intervals after operation, leaving 56 animals on which our results are based. These experiments extended over a period of over three years. The postoperative mortality in the 69 animals not used for analysis in the present series was attributable in a great measure to postoperative peritonitis and surgical shock; a few deaths were due to an overdose of ether (2 animals) or distemper (9 animals). In the surviving dogs, death was generally due to a more or less general debilitated condition

52. Goldberg, S. L.: Intrinsic Regulation of Gastric Acidity, Arch. Int. Med. **49**:816 (May) 1932; Ann. Surg. **96**:155, 1932.

53. Harper, F. R.: Proc. Staff Meet., Mayo Clin. **7**:318, 1932.

54. Matthews, W. B., and Dragstedt, L. R.: Surg., Gynec. & Obst. **55**:265, 1932.

55. A preliminary report was published in 1934 (Ochsner, A.; Gage, M., and Hosoi, K.: Proc. Soc. Exper. Biol. & Med. **31**:1260, 1934).

56. Bass, C. C., and Johns, F. M.: Practical Clinical Laboratory Diagnosis, Baltimore, Williams & Wilkins Company, 1929, chap. 9, p. 104.

induced by repeated feedings of hydrochloric acid, injections of histamine or peptic ulceration. Perforation of an acute or chronic ulcer into the peritoneal or pleural cavity was the cause of sudden death in 10 dogs (peritoneal perforation in 9 and pleural perforation in 1). The animals were generally killed when they were much debilitated, instead of waiting for them to die. They were kept in separate cages, which were cleaned daily. Fresh drip water was a constant source of water supply. On clear sunshiny days the animals were taken out on the roof to bask freely in the sun for several hours. From this it will be seen that poor environmental conditions cannot be said to be of etiologic importance in our experiments.

Necropsy was performed soon after death. Specimens were removed and immediately fixed in 10 per cent neutral solution of formaldehyde or Zenker's fixative. The hematoxylin and eosin stain was used for general cytologic study, and Mallory's aniline blue stain was used for evidence of increased fibrosis as the result of the ulceration. All the lesions described in our experiments were submitted to microscopic study for verification as to whether they were mucosal hemorrhages, erosions or acute or chronic ulcers. Also, for purposes of comparative study to serve as controls, sections were obtained from the gastro-intestinal tracts of presumably healthy dogs which had been electrocuted.

All animals except the controls received thrice daily every other day either a feeding of hydrochloric acid or an injection of from 0.25 to 0.8 mg. of histamine subcutaneously. Four experiments were performed, as follows: experiment 1, in which no surgical procedure was done, to determine the gastric reaction to feeding of hydrochloric acid and injections of histamine; experiment 2, extirpation of (*a*) the greater curvature (fig. 1*a*) and (*b*) the lesser curvature (fig. 2); experiment 3, formation of a gastric pouch from (*a*) the greater curvature (Heidenhain type; fig. 1*b*) or (*b*) the lesser curvature (Pavlov type) plus anastomosis of the proximal jejunum to the pouches (fig. 3), and experiment 4, the same as experiment 3 plus anastomosis of the fundus of the gallbladder to the pouches (figs. 4 and 5). In experiments 2, 3 and 4 control animals were used, which were not given hydrochloric acid or histamine but in which the respective operations were performed. Repeated gastric analyses were carried out preoperatively and postoperatively on all animals.

Postoperatively, irrespective of the character of the operation, the following routine was used: Immediately after the operation, an intravenous infusion of a warmed 5 per cent solution of dextrose in normal lactate-Ringer solution was given into the external jugular vein, about 50 cc. per kilogram of body weight. For the next three days an infusion was given once daily of the same amount of dextrose in lactate-Ringer solution. The animal was allowed nothing by mouth, not even water, during this period. From the fourth to the sixth postoperative day inclusive, the dogs were fed twice daily equal parts of Karo corn syrup and milk and were allowed to drink water. Only rarely did they vomit this milk mixture. The animals that appeared weak, especially after the more prolonged types of operation, were given another three day course of feeding of Karo syrup and milk. Usually on the seventh postoperative day they were returned to the normal stock kennel chow diet of one feeding a day.

EXPERIMENT 1.—*Observations on dogs in which no surgical procedures were carried out, to obtain the gastric reaction to repeated feedings of hydrochloric acid (8 dogs) or injections of histamine (7 dogs):*

Repeated feedings of 1 per cent hydrochloric acid to 6 of 8 fasting dogs produced acute lesions consisting of petechiae, erosions and shallow ulcers in both

the stomach and the duodenum. These acute lesions were present as early as five and eight days after the administration of 1 per cent hydrochloric acid three times daily on alternate days in 2 dogs, respectively. The lesions were usually multiple. Feeding of hydrochloric acid for eight days produced three acute lesions of the stomach and duodenum, proved microscopically, in only 1 of these dogs.

TABLE 1.—*Incidence of Ulcers in Animals Following Feeding with Hydrochloric Acid*

	Acidity Before Administration of 1% Hydrochloric Acid				Acidity After Administration of 1% Hydrochloric Acid Began					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 1	1/13/32	36	24	60	1/21/32	30	23	53	55	Yes
	1/15/32	28	32	60	1/22/32	36	15	51		Erosions
	1/16/32	57	21	78	1/28/32	20	9	29*		
					1/29/32	28	16	44*		
					2/ 4/32	42	18	60*		
					2/ 5/32	39	14	53		
					2/15/32	47	17	64		
					2/19/32	45	15	60*		
					2/25/32	52	40	92		
					3/ 4/32	53	45	98		
					3/10/32	35	29	64		
HH 2	12/23/31	18	10	28	1/21/32	25	18	43	25	No
	1/ 5/32	46	17	63	1/22/32	30	17	47		
	1/ 7/32	35	19	54	1/28/32	37	18	55		
	1/11/32	37	19	56	1/29/32	32	28	60		
	1/12/32	33	6	39	2/ 4/32	26	19	45*		
					2/ 5/32	23	18	41		
HH 3	1/22/32	33	25	58	2/ 4/32	0	21	21	26	Erosions
					2/ 5/32	0	13	13		
HH 23	2/12/32	38	4	42	2/25/32	0	10	10	13	Petechiae
	2/15/32	58	26	84						
	2/18/32	25	10	35						
	2/19/32	31	10	41*						
HH 31	3/ 4/32	15	15	30	3/24/32	0	5	5*	5	Erosion; hemorrhage
	3/10/32	18	4	22						
	3/17/32	9	9	18						
	3/21/32	18	39	57						
HH 32	3/10/32	0	10	10	3/24/32	0	5	5	8	Ulcers of pylorus and duodenum
	3/17/32	15	14	29						
	3/21/32	0	14	14						
HH 41	4/ 1/32	13	5	18	4/ 7/32	0	8	8	13	Erosions of stomach and duodenum
	4/ 4/32	22	10	32	4/15/32	0	8	8*		
					4/21/32	0	9	9*		
HH 42	4/ 1/32	4	4	8	4/ 7/32	21	17	38	13	No
					4/15/32	0	8	8		
					4/21/32	0	23	23		

* Bile.

Although the longest period of experimentation was fifty-five days for this group, ulcers were not obtained in other dogs. Microscopically the mucous cells everywhere in the different sections appeared prominent, with their cell bodies swollen, with a large mucoid globlet pushing the nucleus of the cell to one side and flattening it. This activity of the mucous cells of the stomach to greater production of mucus

TABLE 2.—*Incidence of Ulcers in Animals Following the Administration of Histamine Subcutaneously*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine Began					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 4	12/32/31	33	28	61	1/21/32	37	23	60	155	No; gastritis
	1/ 5/32	21	11	32	1/22/32	5	10	15		
	1/ 7/32	20	6	26	1/28/32	18	3	21		
	1/11/32	8	3	11	1/29/32	38	16	54		
	1/12/32	32	8	40	2/ 4/32	43	23	66		
Received histamine					2/ 5/32	16	8	24		
1/13 to 2/ 2/32, 0.04 mg. per Kg. daily					2/15/32	18	15	33		
2/ 3 to 2/19/32, 0.08 mg. per Kg. daily					2/19/32	40	17	57		
2/20 to 3/22/32, 0.6 mg. per Kg. every 2 days					2/25/32	82	22	104		
3/24 to 6/16/32, 0.8 mg. per Kg. every 2 days					3/ 4/32	24	9	33		
					3/10/32	32	11	43		
					3/18/32	22	11	33		
					3/24/32	45	5	50		
					4/ 1/32	47	11	58		
					4/ 7/32	35	9	44		
					4/15/32	52	15	67		
					4/21/32	39	12	51		
					4/29/32	35	34	69		
					5/ 5/32	60	18	78		
					5/11/32	33	11	44		
					5/19/32	49	19	68		
					5/27/32	38	14	52		
					6/ 2/32	35	23	58		
					6/10/32	23	10	33		
HH 5	12/23/31	46	16	62	1/21/32	0	27	27	55	Hemorrhages
	1/ 5/32	27	17	44	1/22/32	23	21	44		
	1/ 7/32	25	13	38	1/28/32	33	32	65		
	1/11/32	71	64	135	1/29/32	28	30	58		
	1/12/32	29	9	38	2/ 4/32	33	45	78		
Received histamine					2/ 5/32	32	28	60		
1/13 to 2/ 2/32, 0.04 mg. per Kg. daily					2/15/32	10	15	25		
2/ 3 to 2/19/32, 0.08 mg. per Kg. daily					2/19/32	30	10	40		
2/21 to 3/ 4/32, 0.6 mg. per Kg. every 2 days					2/25/32	55	22	77		
					3/ 4/32	41	10	51		
HH 6	12/23/31	0	31	31	1/21/32	60	15	75	28	Gastritis
	1/ 5/32	43	20	63	1/22/32	35	11	46		
	1/ 7/32	52	12	64	1/28/32	26	5	31		
	1/11/32	5	8	13	1/29/32	68	17	85		
	1/12/32	28	15	43						
Received histamine										
1/13 to 2/9/32, 0.04 mg. per Kg. daily										
HH 25	2/12/32	30	19	49	2/25/32	35	15	50	14	Ulcers; gastritis
	2/15/32	23	19	42	3/ 4/32	22	16	38		
	2/18/32	35	11	46						
	2/19/32	42	20	62						
Received histamine										
0.6 mg. per Kg. every 2 days										
HH 33	3/10/32	20	14	34	3/24/32	21	9	30	7	Petechiae; ulcers of stomach and duodenum; gastritis; duodenitis
	3/17/32	22	16	38						
	3/21/32	0	11	11						
Received histamine										
0.6 mg. per Kg. every 2 days										
HH 36	3/17/32	0	19	19	3/24/32	72	12	84	27	Hemorrhages; erosions; gastritis
	3/21/32	19	16	35						
Received histamine										
0.8 mg. per Kg. every 2 days										
HH 43	4/ 1/32	13	10	23	4/ 7/32	33	12	45	134	Ulcers; hemorrhages; gastritis
	4/ 4/32	34	26	30	4/15/32	35	10	45		
					4/21/32	43	11	54		
Received histamine					4/29/32	53	10	63		
0.8 mg. per Kg. every 2 days					5/ 5/32	41	18	59		
					5/11/32	51	11	62		
					5/19/32	53	10	63		
					5/27/32	37	11	48		
					6/ 2/32	38	13	51		
					6/10/32	45	15	60		
					6/16/32	38	22	60		
					6/24/32	12	76	88		
					6/30/32	35	33	68		
					7/ 8/32	19	16	35		
					7/14/32	34	41	75		
					7/22/32	10	28	38		
					7/28/32	30	22	52		
					8/ 5/32	29	15	44		
					8/11/32	21	19	40		
					8/19/32	51	22	73		

may be one reason that more ulcers did not develop. This method of feeding hydrochloric acid failed to produce any chronic ulcers, as proved by microscopic study of the ulcers. In 6 dogs there was associated mild to marked gastritis and duodenitis, whereas in 2 of the 8 animals no lesions demonstrable either grossly or microscopically were evident, even after experimental periods of thirteen and twenty-five days, respectively. In any study of gastric analysis in dogs it must be remembered that values for acidity are extremely variable, in that normal values for acidity may be obtained one day and subnormal values or even hyperacidic values the next day (table 1). It has been shown repeatedly and statistically by

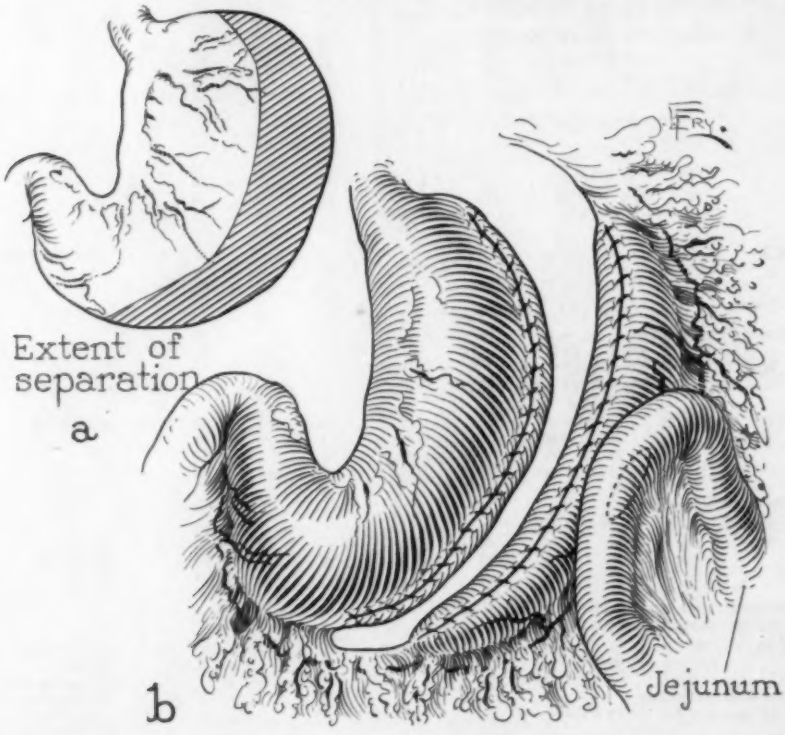

Fig. 1.—The drawing in the upper left hand corner (*a*) shows the extent of resection of the region of the greater curvature or the amount of the stomach to be incorporated into a gastric pouch. The larger drawing (*b*) illustrates the formation of a pouch from the greater curvature, with a side-to-side anastomosis of a loop of the proximal jejunum to this pouch.

Laspeyres [57] and others that even in human beings this variability from anacidity to hyperacidity obtains in persons both in health and in disease, though to a less extent than in animals. This variability has been demonstrated in our own experiments in the gastric analyses on the controls. However, a study of the acidity values for the entire period of experimentation with repeated feeding

57. Laspeyres, R.: Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **5**:25, 157 and 225, 1902.

of hydrochloric acid showed that in general there was a tendency toward achlorhydria; chlorides continued to be secreted, but at a low level (table 1). No acceptable explanation has as yet been given as to why under certain conditions the stomach loses its ability to secrete free hydrochloric acid but is still able to secrete chlorides. But there was a return to normal values for free hydrochloric acid after a month or so of experimentation, even though the administration of hydrochloric acid was not stopped. Thus, it is seen that the parietal cells of the stomach recover from the toxic or corrosive effect of the repeated feedings. The highly corrosive concentration of acid used experimentally by others and by us can never obtain in the human stomach, even in disease, because the intrinsic or extrinsic mechanisms of neutralization rapidly reduce any high acidity to 0.15 per cent hydrochloric acid.

Injections of histamine in 7 animals caused varying degrees of anemia of the tissues. In contrast to the pink appearance of tissues of presumably healthy dogs, the various viscera appeared very pale in the dogs treated with histamine. From a mild to marked gastritis and duodenitis were present in all 7 (100 per cent) animals, and in 1 these conditions were the only demonstrable disturbance, even after five months' experimentation with histamine. The gastritis appeared to be limited to the pyloric antrum and involved the entire stomach only when it was present to a marked degree. There were also hemorrhages (4 dogs), erosions (1 dog) and acute ulcers (3 dogs, or 43 per cent), which were usually multiple. In one animal (HH 43), which had received injections over a period of one hundred and thirty-four days, there were twenty-two ulcers of various sizes and depths (fig. 6). These ulcers were most frequently or most abundantly found along the lesser curvature, confirming the usual clinical observation that peptic ulcers occur along the lesser curvature of the pylorus. Histamine was found to produce ulcers but did not stop them from healing, as evidenced by the microscopic picture of encroachment of marginal epithelium over the floor of the ulcer. Also, there was microscopic evidence of increased production of mucus, shown by the prominence everywhere of the distended mucous cells of the gastric mucosa. Histamine does not appear to cause hyperacidity or hypo-acidity of exhaustion, even after from four to five months of injections (table 2). The values for acidity obtained were usually within the range of normal variations for dogs (table 2), although the values after stimulation with histamine in dogs with a pouch with anastomosis from the pouch to the jejunum were frequently double the preoperative values without histamine stimulation. Gastric analyses in at least 2 animals (HH 50 and 83) showed this definitely.

EXPERIMENT 2.—*Observations on dogs with extirpated (a) greater curvature (fig. 1a) and (b) lesser curvature (fig. 2).*

The greater curvature of the stomach was extirpated in 30 animals, only 11 of which lived sufficiently long for satisfactory observations to be made. The lesser curvature was extirpated in 6 animals, 4 of which survived long enough for sufficient observations. Practically all the respective curvatures were extirpated, the actual amount removed depending almost entirely on the size of the stomach. Black silk sutures were used throughout, but later all hemostatic sutures were made with no. 0 chromic catgut, the silk being employed only for the seromuscular layer. Extirpation of the greater or lesser curvatures of the stomach in dogs did not significantly change the values for acidity of the gastric contents of the main portion of the stomach when compared with the preoperative values (tables 3 and 4). In the control groups of animals receiving no hydrochloric acid or hista-

TABLE 3.—*Preoperative and Postoperative Values for Hydrochloric Acid After a Test Meal in Animals Following Resection of the Greater Curvature of the Stomach*

	Preoperative Controls				Postoperative Controls					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 16	1/21/32	35	28	63	2/25/32	11	9	20*	33	Ulcers
	1/22/32	27	12	39	3/ 4/32	18	16	34		
	1/28/32	14	9	23*	3/10/32	0	9	9		
	1/29/32	45	11	56*	3/17/32	0	4	4		
	2/ 4/32	40	19	59	3/24/32	25	12	37		
	2/ 5/32	20	10	30						
HH 18	1/22/32	50	17	67	2/25/32	15	18	33	16	None; anemia
	1/28/32	55	10	65	3/ 4/32	25	7	32		
	1/29/32	42	5	47*	3/10/32	27	12	39		
	2/ 4/32	55	10	65*						
	2/ 5/32	42	11	53*						
HH 34	3/10/32	21	23	44	4/ 7/32	49	19	68	103	None
	3/17/32	33	25	58	4/15/32	39	15	54		
	3/21/32	36	11	47	4/21/32	29	21	50		
					4/29/32	40	24	64		
					5/ 5/32	0	42	42		
					5/11/32	70	17	87		
					5/19/32	63	18	81		
					5/27/32	35	18	53		
					6/ 2/32	57	20	77		
					6/10/32	32	12	44		
					6/16/32	55	18	73		
					6/24/32	55	18	73		
					6/30/32	53	17	70		
					7/ 8/32	28	24	52		
					7/14/32	20	5	25		
HH 37	3/17/32	35	25	60	4/ 7/32	55	25	80	47	Ulcers of pylorus
	3/21/32	36	30	66	4/ 9/32	33	23	56		
					4/21/32	32	32	64		
					4/29/32	21	29	50		
					5/ 5/32	37	30	67		
					5/11/32	44	37	81		
					5/19/32	38	12	50		

* Bile.

TABLE 4.—*Preoperative and Postoperative Values for Hydrochloric Acid After a Test Meal in Animals Following Resection of the Lesser Curvature of the Stomach*

	Preoperative Controls				Postoperative Controls					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 74	8/15/33	20	19	39	9/ 7/33	0	14	14*	84	None
	8/17/33	14	17	31	10/ 5/33	30	10	40		
					10/13/33	0	10	10*		
					10/19/33	0	10	10*		
					10/27/33	40	25	65		
					11/ 2/33	39	12	51		
					11/10/33	18	10	28		
HH 107	11/ 9/33	8	8	16	12/ 1/33	0	5	5*	65	None
	11/10/33	14	4	18	12/ 8/33	5	5	10		
					12/14/33	49	11	60		
					12/22/33	0	17	17*		
					12/28/33	16	24	40		
					1/ 5/34	0	5	5*		
					1/11/34	8	10	18*		
					1/19/34	7	16	23		
HH 106	11/ 9/33	22	14	36	12/ 1/33	0	5	5*	13	None
	11/10/33	0	10	10*						

* Mucus.

mine ulcers did not develop in the 3 in which the lesser curvature was resected and did develop in 2 (50 per cent) of the 4 in which the greater curvature was resected.

Feeding of hydrochloric acid to dogs with extirpation of the greater curvature produced multiple erosions of the pylorus in 2 of 3 dogs (HH 24 and 46). In the third dog (HH 44), with no erosions, moderate gastritis of the pyloric mucosa was found. This is interesting, because this particular dog received 1 per cent hydrochloric acid by stomach tube three times daily every other day for forty-seven days. A study of the gastric analyses performed one hour after the feeding of hydrochloric acid shows that the dog's stomach was able to neutralize rapidly this concentration of acid to within normal limits (table 5). Regurgitation of bile is probably not a factor in this neutralization, since no bile was found in the

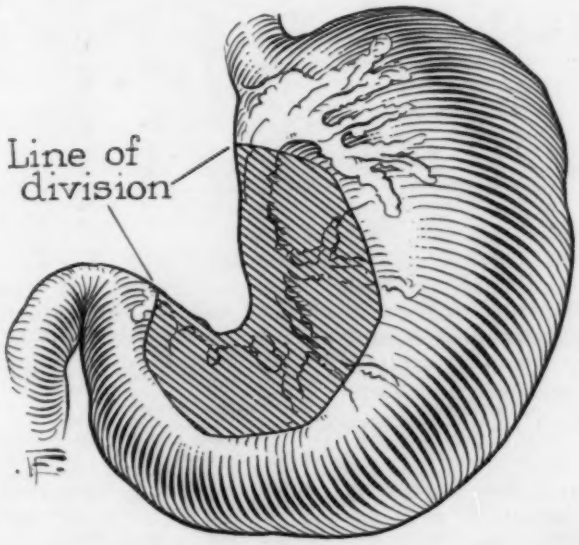

Fig. 2.—A drawing showing the extent of extirpation of the region of the lesser curvature or the amount of the region of the lesser curvature to be incorporated into a gastric pouch.

21 samples of the gastric contents in this control group (3 animals) receiving hydrochloric acid and since the combined values for hydrochloric acid were always lower than those for free hydrochloric acid in 2 (HH 24 and 44) of the 3 animals. After stimulation with histamine the values for acidity remained within normal limits (table 6), and acute ulcers were produced in 2 (HH 40 and 15) of 4 dogs with extirpation of the greater curvature, 1 of which also showed acute erosions (HH 40). After repeated stimulation with histamine no erosions or ulcers were found (table 7) in 1 animal (HH 101) with extirpation of the lesser curvature. Stimulation with histamine evidently did not increase the incidence of gastric erosions or ulcerations in this group. The absence of erosions or ulcerations in the group with extirpation of the lesser curvature and their formation in the group with extirpation of the greater curvature appear to support the theory

TABLE 5.—*Incidence of Ulcers in Animals with the Greater Curvature of Stomach Removed Following Feeding with Hydrochloric Acid*

	Acidity Before Administration of 1% Hydrochloric Acid				Acidity After Administration of 1% Hydrochloric Acid					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 24	2/12/32	29	21	50	3/24/32	15	17	32	67	Erosions; gastritis; duodenitis
	2/15/32	48	16	64	4/ 1/32	50	11	61		
	2/18/32	10	16	26	4/ 7/32	49	9	58		
	2/19/32	25	22	47	4/15/32	27	14	41		
	2/25/32	40	11	51	4/21/32	31	12	43		
					4/29/32	35	15	50		
					5/ 5/32	18	15	33		
					5/11/32	41	13	54		
					5/19/32	35	10	45		
HH 44	4/ 1/32	38	16	54	4/21/32	40	19	59	47	Gastritis
	4/ 4/32	63	21	84	4/29/32	15	10	25		
					5/ 5/32	22	19	41		
					5/11/32	11	12	23		
					5/19/32	27	13	40		
					5/27/32	14	9	23		
					6/ 2/32	20	10	30		
HH 46	4/ 7/32	56	28	84	5/ 5/32	0	21	21	37	Erosions; gastritis
	4/12/32	29	21	50	5/11/32	0	11	11		
					5/19/32	9	16	25		
					5/27/32	16	14	30		
					6/ 2/32	6	16	22		

TABLE 6.—*Incidence of Ulcers in Animals with the Greater Curvature of the Stomach Removed Following the Subcutaneous Injection of Histamine*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 39	3/17/32	13	12	25	4/15/32	0	13	13*	120	Gastritis
	3/21/32	9	12	21	4/21/32	57	18	75		
					4/29/32	62	20	82		
					5/ 5/32	39	22	61		
					5/11/32	28	22	50		
					5/19/32	30	13	43		
					5/27/32	28	12	40		
					6/ 2/32	33	9	42		
					6/10/32	28	10	38		
					6/16/32	65	13	78		
					6/24/32	38	10	48		
					6/30/32	30	14	44		
					7/ 8/32	15	10	25		
					7/14/32	29	20	49		
					7/22/32	32	22	54		
					7/28/32	22	14	36		
					8/ 5/32	39	23	62		
HH 40	3/17/32	20	12	32	4/15/32	0	31	31	13	Ulcers; erosions
	3/21/32	20	11	31	4/21/32	6	24	30		
HH 45	4/ 1/32	14	51	65	4/21/32	5	11	16	16	Gastritis
	4/ 4/32	18	19	37	4/29/32	0	26	26		
HH 15	1/ 5/32	0	29	29	2/15/32	41	20	61	27	Ulcers
	1/ 7/32	39	16	55	2/19/32	15	20	35		
	1/11/32	18	18	36	2/25/32	54	32	86		
	1/12/32	4	22	26	3/ 4/32	57	18	75		

* Bile.

that the resection of the regions of the lesser curvature at the angle of reentrance prevents the formation of peptic ulcer.

EXPERIMENT 3.—*Observations on dogs with a Heidenhain (fig. 1b) or Pavlov pouch (fig. 3).*

A pouch of the greater curvature (Heidenhain) with jejunal anastomosis was made in 6 animals, all of which survived sufficiently long for the observations

TABLE 7.—*Incidence of Ulcers in Animals with the Lesser Curvature of the Stomach Removed Following the Subcutaneous Administration of Histamine*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 101	10/13/33	25	20	45	11/16/33	20	12	32	62	None
	10/17/33	30	15	45	11/24/33	10	10	20*		
					12/ 1/33	0	90	90		
Postoperative values					12/ 8/33	13	8	21		
	11/15/33	8	14	22	12/14/33	15	20	35		
					1/ 5/34	31	9	40		
					1/11/34	31	22	53		

* Mucus.

TABLE 8.—*Incidence of Ulcers in Animals with Heidenhain Pouch of the Greater Curvature of the Stomach Anastomosed to the Jejunum Following the Administration by Mouth of Dilute Hydrochloric Acid*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 49	5/27/32	29	18	47	6/24/32	0	11	11	11	Erosions and ulcers of jejunum
	6/ 2/32	37	17	54	6/30/32	0	18	18*		
HH 50	6/23/32	6	6	12	7/22/32	17	23	40	64	Ulcers of pylorus; gastritis; perforated jejunal ulcer
	6/24/32	14	6	20	7/28/32	5	10	15		
					8/ 5/32	Entirely mucus				
Postoperative values					8/11/32	7	41	48		
	7/ 8/32	13	12	25	8/19/32	25	21	46		
	7/14/32	0	29	29	8/25/32	26	17	43		
					9/ 2/32	20	47	67		
					9/ 8/32	25	24	49		
					9/16/32	45	10	55		
HH 51	5/19/32	21	37	58	6/24/32	42	22	64	64	Gastritis; erosion of duodenum; marginal and jejunal ulcers
	5/27/32	13	11	24	6/30/32	31	10	41		
					7/ 8/32	19	19	38		
					7/14/32	30	37	67		
					7/22/32	35	28	63		
					7/28/32	36	22	58		
					8/ 5/32	22	17	39		
					8/11/32	21	21	42		
					8/19/32	42	16	58		
					8/25/32	18	10	28		

* Mucus.

to be completed. A pouch of the lesser curvature (Pavlov) with jejunal anastomosis was made in 27 animals, only 7 of which lived sufficiently long for observations to be made. In our experiments with the pouch of the greater curvature (modified Heidenhain type) with jejunal anastomosis (simulating Meckel's diver-

ticulum containing gastric mucosa), acute, subacute or chronic jejunal ulcers were produced in each of 6 animals (100 per cent). The ulcers were in the efferent loop in 5 dogs and both in the efferent loop and at the anastomotic stoma in 1 dog (HH 51). These ulcers had a tendency to perforate, since 5 of the 6 animals died of peritonitis following perforation (fig. 7). Stimulation with histamine did not increase this tendency to perforation of an anastomotic ulcer, as 2 of 3 dogs receiving histamine had perforated jejunal ulcers whereas all 3 control animals, which did not receive histamine, had perforated ulcers. In 1 (HH 47) of these control animals, there were two chronic gastric ulcers (located in the main portion of the stomach) in addition to the perforated jejunal ulcer. Gastric analyses showed values for acidity to be within normal variations (tables 8 and 9). Stimulation with histamine did not prevent an anastomotic ulcer from undergoing

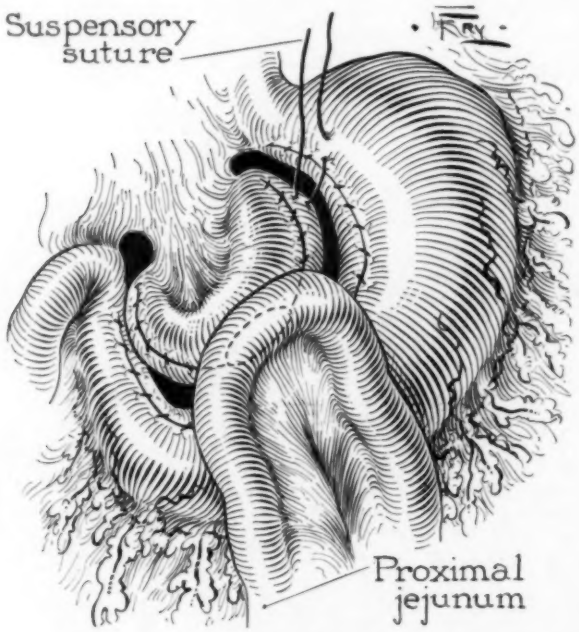

Fig. 3.—A drawing showing the formation of a gastric pouch from the lesser curvature and anastomosis of a loop of the proximal jejunum. Note the suspensory suture to prevent the pouch from being pulled or stretched subsequently.

a healing process, as shown by the microscopic study of one of these jejunal ulcers. The animal (HH 49) in which there was this tendency of the ulcer to heal had been receiving 0.8 mg. of histamine per kilogram of body weight three times daily on alternate days during a period of eleven days. Because of the predilection of jejunal ulcers for the efferent loop, a careful study of the jejunal loop anastomosed to the gastric pouch was made. It was noted that the proximal or afferent loop was always normal in appearance, whereas the distal or efferent loop showed the effects of the irritating acid secretions from the gastric pouch passing through it. The efferent loop was edematous and congested, with numerous various-sized petechiae and hemorrhages and even erosions. Microscopic studies revealed subacute or chronic jejunitis, depending on the duration of the experiment.

TABLE 9.—*Incidence of Ulcers in Control Animals with Heidenhain Pouch of the Greater Curvature of the Stomach Anastomosed to the Jejunum*

	Preoperative Controls				Postoperative Controls					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 47	5/19/32	28	8	36	6/24/32	10	16	26	78	Ulcers of pylorus; perforated jejunal ulcer
	5/27/32	9	13	22	6/30/32	18	29	47		
	6/ 9/32	11	31	42	7/ 8/32	20	15	35		
	6/10/32	28	15	43	7/14/32	5	25	30		
					7/22/32	5	24	29		
					7/26/32	23	22	45		
					8/ 5/32	40	18	58		
					8/11/32	20	22	42		
					8/19/32	48	19	67		
					8/25/32	33	19	52		
					9/ 2/32	15	17	32		
HH 48	5/19/32	5	10	15	6/24/32	18	20	38	71	Perforated jejunal ulcer
	5/27/32	18	28	46	6/30/32	23	20	43		
					7/ 8/32	5	25	30		
					7/22/32	37	17	54		
					7/26/32	24	15	39		
					8/ 5/32	19	7	26		
					8/11/32	32	21	53		
					8/19/32	20	14	34		
					8/25/32	27	13	40		
					9/ 2/32	23	27	50		
HH 52	5/19/32	33	5	38	Died 6/23/32 just after rest period, 16 days postoperatively					Perforated jejunal ulcer
	5/27/32	22	10	32						

TABLE 10.—*Incidence of Ulcers in Animals with Modified Pavlov Pouch of the Lesser Curvature of the Stomach Anastomosed to the Jejunum Following the Administration of Histamine Subcutaneously*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 83	9/ 8/33	10	10	20	10/ 5/33	75	20	95	27	Ulcers of jejunum; perforated jejunal ulcer
	9/12/33	5	10	15	10/13/33	12	18	30		
					10/19/33	0	42	42		
HH 93	9/15/33	37	18	55	10/ 9/33	20	15	35	24	Perforated jejunal ulcer
	9/19/33	46	14	60	10/13/33	0	20	20*		
					10/19/32	0	10	10*		
					10/27/33	0	10	10*		
HH 89	9/15/33	18	7	25	10/13/33	7	23	30	157	Ulcer of jejunum
	9/19/33	44	22	66	10/19/33	21	11	32		
					10/27/33	13	47	60		
Postoperative values					11/ 2/33	28	18	46		
	10/ 5/33	30	15	45	11/10/33	10	14	24		
					11/16/33	0	58	58		
					11/24/33	35	12	47		
					12/ 1/33	15	28	43		
					12/ 8/33	41	17	58		
					12/14/33	45	25	70		
					12/22/33	22	18	40		
					12/28/33	16	8	24		
					1/ 5/34	29	30	59		
					1/11/34	64	24	88		
					1/19/34	71	21	92		
					1/25/34	60	20	80		
					2/ 2/34	52	34	86		
					2/ 8/34	41	23	64		
					2/16/34	23	9	32		
					2/22/34	49	9	58		
					3/ 2/34	37	8	45		

* Mucus.

TABLE 11.—*Incidence of Ulcers in Control Animals with Modified Pavlov Pouch of the Lesser Curvature of the Stomach Anastomosed to the Jejunum*

	Preoperative Controls				Postoperative Controls					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 86	9/ 8/33	16	9	25	10/ 5/33	61	25	86	69	None
	9/12/33	0	64	64	10/13/33	22	16	38		
					10/19/33	50	35	85		
					10/27/33	45	15	60		
					11/ 2/33	30	10	40		
					11/10/33	30	18	48		
					11/16/33	45	49	94		
					11/24/33	49	15	64		
					12/ 1/33	60	20	80		
					12/ 8/33	42	9	51		
					12/14/33	35	80	115		
					12/22/33	67	32	99		
					12/28/33	0	87	87		
					1/ 5/34	60	21	81		
					1/11/34	0	82	82*		
HH 87	9/ 8/33	10	10	20	10/ 5/33	0	5	5*	81	None
	9/12/33	5	10	15	10/13/33	15	5	20		
					10/19/33	14	8	22		
					10/27/33	0	63	63*		
					11/ 2/33	5	5	10		
					11/10/33	10	5	15		
					11/16/33	0	60	60		
					11/24/33	10	20	30		
					12/ 1/33	27	24	51		
					12/ 8/33	5	20	25		
					12/14/33	37	15	52		
					12/22/33	7	4	11		
					12/28/33	5	6	11		
					1/ 5/34	23	19	42		
					1/11/34	10	10	20		
					1/19/34	12	5	17		
HH 88	9/ 8/33	0	5	5	10/ 5/33	81	14	95	152	Ulcers of jejunum
	9/12/33	0	75	75	10/13/33	18	12	30		
					10/19/33	55	21	76		
					10/27/33	35	10	45		
					11/ 2/33	15	10	25		
					11/10/33	33	16	49		
					11/16/33	25	18	43		
					11/24/33	65	24	89		
					12/ 1/33	18	37	55		
					12/ 8/33	35	19	54		
					12/14/33	52	13	65		
					12/22/33	23	15	38		
					12/28/33	5	46	51		
					1/ 5/34	83	10	93		
					1/11/34	83	11	94		
					1/19/34	11	27	38		
					1/25/34	9	43	52*		
					2/ 2/34	0	52	52†		
					2/ 8/34	4	8	12		
					2/16/34	35	22	57		
					2/22/34	50	13	63		
HH 77	9/ 7/33	20	22	42	Died 9/19/33 during rest period, 8 days postoperatively					Hemorrhagic erosions; perforated marginal ulcer
	9/ 8/33	14	17	31						

* Mucus. † Food.

In the experiments with the pouch of the lesser curvature (modified Pavlov type) with jejunal anastomosis (thus simulating Meckel's diverticulum containing gastric mucosa), chronic jejunal ulcers were present in all 3 dogs that received histamine, and no jejunal ulcers were present in 2 of 4 control dogs that did not receive histamine (tables 10 and 11). In the experiments on the lesser curvature with jejunal anastomosis there were seven jejunal ulcers, four of which were located in the efferent loop of the jejunum, two opposite the stoma and one at the margin. Two of the ulcers in the efferent loop (HH 83 and 93) and one marginal ulcer (HH 77) perforated (fig. 8). The two jejunal ulcers, shown in figure 9, showed healing, which was verified microscopically. This series of experi-

TABLE 12.—*Incidence of Ulcers in Animals with Modified Heidenhain Pouch of the Greater Curvature of the Stomach Anastomosed to the Jejunum and the Gallbladder Following the Administration of Histamine Subcutaneously, the Bile Acting as a Buffer to the Hydrochloric Acid in the Pouch*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 66	1/12/33	22	17	39	2/ 3/33	0	20	20	30	Hemorrhages
	1/13/33	47	18	65	2/ 9/33	100	6	106		
					2/17/33	100	10	110		
					2/23/33	51	20	71		
HH 69	7/26/33	18	12	30	8/11/33	14	21	35	27	None
	7/27/33	35	30	65	8/17/33	0	40	40		
					8/25/33	34	29	63		
HH 75	8/23/33	37	18	55	9/15/33	85	11	96	15	Ulcers of jejunum; perforated jejunal ulcer
	8/25/33	10	63	73	9/21/33	89	11	100		
HH 76	8/30/33	0	26	26	9/21/33	30	13	43	127	Ulcer of jejunum
	8/31/33	36	16	52	9/29/33	5	20	25		
					10/ 5/33	50	10	60		
					10/13/33	20	20	40		
					10/19/33	51	9	60		
					10/27/33	44	16	60		
					11/ 2/33	50	10	60		
					11/10/33	35	12	47		
					11/16/33	8	77	85		
					11/24/33	27	18	45		
					12/ 1/33	44	31	75		
					12/ 8/33	33	16	49		
					12/14/33	55	30	85		
					12/22/33	55	35	90		
					12/28/33	21	45	66		
					1/ 5/34	18	10	38		
					1/11/34	36	15	51		

ments in which Meckel's diverticulum containing gastric mucosa was simulated showed that an unneutralized acid secretion flowing into the jejunum, usually not accustomed to being bathed in such an acid fluid, may cause true ulceration of the jejunal mucosa. It confirms the clinical observation that the presence of gastric mucosa in Meckel's diverticulum may lead to ulceration of the intestinal mucosa.

EXPERIMENT 4.—*Observations on dogs with the fundus of the gallbladder anastomosed to (a) the Heidenhain pouch (fig. 4) and (b) the Pavlov pouch (fig. 5).*

A pouch of the greater curvature (Heidenhain pouch) with anastomoses to the jejunum and gallbladder was made in 23 dogs, 7 of which lived long enough for completion of observations (tables 12 and 13). A pouch of the lesser curvature

(Pavlov) with anastomoses to the jejunum and gallbladder was made in 18 animals, of which only 6 lived sufficiently long for completion of observations (tables 14 and 15). Bile prevented the postoperative anastomotic ulcer from forming in the 3 dogs with the Heidenhain pouch in which the jejunum and the gallbladder had been anastomosed, but it did not prevent the formation of chronic anasto-

TABLE 13.—*Incidence of Ulcers in Control Animals with Modified Heidenhain Pouch of the Greater Curvature of the Stomach Anastomosed to the Jejunum and Gallbladder*

	Preoperative Controls				Postoperative Controls					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 59	6/23/32	20	14	34	7/ 8/32	0	5	5*	112	Hemorrhages of stomach; erosions of stomach
	6/24/32	21	14	35	7/14/32	5	25	30		
					7/22/32	5	16	21		
					7/26/32	25	22	47		
					8/ 5/32	10	13	23		
					8/19/32	34	14	48		
					8/25/32	33	17	50		
					9/ 2/32	0	17	17		
					9/ 8/32	0	44	44		
					9/22/32	0	73	73		
					10/ 1/32	16	12	28		
					10/ 6/32	23	16	39		
					10/14/32	18	14	32		
					10/21/32	12	14	26		
HH 70	2/23/33	22	8	30	5/12/33	12	12	24	81	Gastritis
					5/18/33	29	22	51		
					5/26/33	64	31	95		
					6/ 1/33	76	20	96		
					6/ 9/33	80	6	86		
					6/15/33	59	19	78		
					6/23/33	40	6	46		
					6/29/33	39	14	53		
					7/ 7/33	40	60	100		
					7/13/33	52	20	72		
					7/22/33	45	20	65		
HH 68	1/27/33	0	12	12	2/23/33	57	13	70	160	Gastritis
	2/ 3/33	40	5	45	3/ 3/33	15	5	20		
					3/ 8/33	0	22	22*		
					3/17/33	0	30	30*		
					3/23/33	13	22	35		
					3/31/33	0	46	46		
					4/ 6/33	58	32	90		
					4/20/33	0	34	34		
					4/28/33	23	27	50		
					5/ 4/33	14	31	45		
					5/12/33	0	55	55		
					5/18/33	46	19	65		
					5/26/33	32	28	60		
					6/ 1/33	14	16	30		
					6/ 9/33	0	40	40		
					6/15/33	6	17	23		
					6/23/33	26	12	38		
					6/29/33	0	47	47		
					7/ 7/33	0	29	29		
					7/13/33	15	10	25		
					7/22/33	14	8	22		
					7/27/33	15	8	23		

* Mucus.

motic ulcer after stimulation with histamine in 2 (HH 75 and 76) of the 4 dogs that received histamine. There were three jejunal ulcers in the 2 dogs, one each in the afferent and the efferent loop of the jejunum and one opposite the gastrojejunal stoma (fig. 10). It was the ulcer in the efferent loop that perforated. In both of these animals the stimulation with histamine produced high values for acidity as compared with the preoperative values. All 7 dogs

TABLE 14.—*Incidence of Ulcers in Animals with a Modified Pavlov Pouch of the Lesser Curvature of the Stomach Anastomosed to the Jejunum and the Gallbladder Following the Subcutaneous Administration of Histamine*

	Acidity Before Injections of Histamine				Acidity After Injections of Histamine					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 87	9/ 8/33	10	10	20	2/ 2/34	23	9	32	62	None
	9/12/33	5	10	15	2/ 6/34	25	10	35		
					2/ 8/34	48	15	63		
					2/16/34	59	14	73*		
					2/22/34	40	9	49		
					3/ 2/34	18	24	42		
HH 118	11/30/33	14	14	28	1/25/34	5	36	41	61	None
	12/ 8/33	14	6	20	2/ 1/34	4	12	16		
	12/28/33	19	22	41	2/ 8/34	14	10	24		
					2/16/34	18	4	22		
Postoperative values					2/22/34	8	10	18		
	1/24/34	8	14	22	3/ 2/34	5	5	10		
HH 121	12/21/33	8	7	15	1/25/34	50	16	66	28	None
	12/22/33	8	12	20	2/ 2/34	33	11	44		
Postoperative values					2/ 8/34	57	14	71		
	1/23/34	14	11	25	2/16/34	58	14	72		

* Bile.

TABLE 15.—*Incidence of Ulcers in Control Animals with a Modified Pavlov Pouch of the Lesser Curvature of the Stomach Anastomosed to the Jejunum and the Gallbladder*

	Preoperative Controls				Postoperative Controls					
		Hydrochloric Acid				Hydrochloric Acid				
Dog	Date	Free	Combined	Total	Date	Free	Combined	Total	Duration, Days	Ulcer
HH 106	11/ 9/33	20	18	38	12/15/33	5	7	12	50	Marginal ulcer;
	11/10/33	10	5	15	12/22/33	5	70	75		perforated
					1/ 5/34	0	87	87		jejunal ulcer
					1/19/34	12	29	41		
HH 113	12/ 1/33	10	5	15	Died 1/5/34 during rest period, 10 days postoperatively					Perforated marginal ulcer; duodenal ulcer
	12/ 8/33	27	22	49						
HH 120	12/21/33	15	6	21	1/23/34	50	11	61	49	Erosions,
					1/25/34	8	35	43*		ulcers and
					2/ 2/34	30	21	51		hemorrhages
					2/ 8/34	8	4	12		of stomach;
					2/16/34	21	11	32		ulcer of
					2/22/34	57	35	92		jejunum

* Mucus.

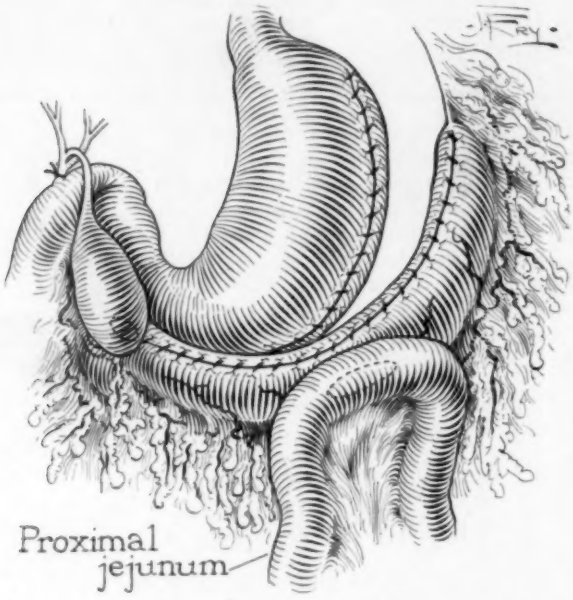

Fig. 4.—A drawing showing the formation of a gastric pouch from the greater curvature and anastomosis of the proximal jejunal loop and fundus of the gallbladder to this pouch. The common bile duct is sectioned and doubly ligated.

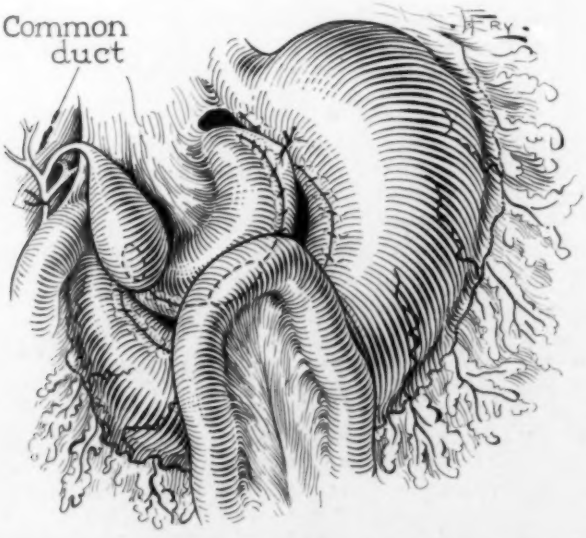

Fig. 5.—A drawing showing the formation of a gastric pouch from the lesser curvature and anastomosis of the proximal jejunum and fundus of the gallbladder to this pouch. The common bile duct is sectioned and doubly ligated.

Fig. 6 (dog HH 43).—Histamine was injected three times daily on alternate days for a period of one hundred and thirty-four days. The stomach was opened along the greater curvature. The pyloric regions and the duodenum were pale in comparison with the fundus, which was markedly injected. Note that most of the erosions and acute ulcerations are in the pyloric antrum. About twenty-two acute ulcers can be counted.

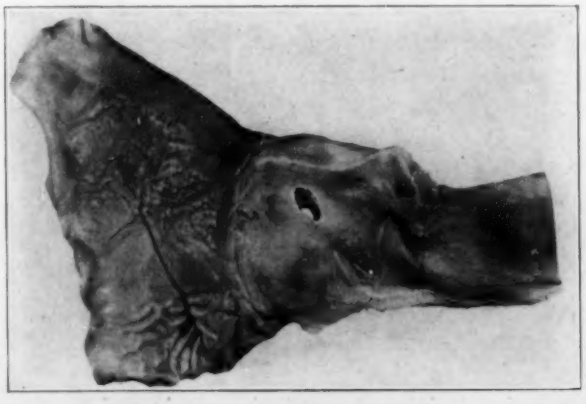

Fig. 7 (dog HH 52).—A control animal, observed for fourteen days post-operatively. The anastomosis between the gastric pouch and jejunum has been cut open. On the jejunal side there is a large perforation in the center of an extensive ulceration.

in this group had a mild to moderate jejunitis of the efferent loop in spite of the more or less neutralizing effect of the bile. In the 3 dogs with a modified Pavlov pouch in which no histamine was used bile flowing through the anastomosis did not prevent the formation of jejunal ulcers. There was a total of four ulcers, one acute and three chronic. As regards location, two were in the margin, one in the efferent loop and one opposite the stoma. The ulcers in 2 of these animals (HH 106 and 113) perforated (fig. 11). The greater secretory activity of this Pavlov type of pouch because of its intact vagal nerve supply may be surmised to be one factor in the production of ulceration in some instances. As regards the lesions of the stomach or duodenum itself, deviation of the bile toward the pouch in 13 dogs produced hemorrhages and erosions of the main portion of the stomach in only 1 animal (HH 120), a duodenal ulcer in another (HH 113) and a small pyloric mucosal hemorrhage in 1 that received histamine.

COMMENT

Gastric Ulceration.—It is significant in the experiments on extirpation of the curvature that the incidence of ulceration and erosion in the lesser curvature after the extirpation of the greater curvature was 63.6 per cent, whereas no ulcers or erosions occurred in the remaining greater curvature after extirpation of the lesser curvature. These facts, together with the observation that following the injection of histamine multiple ulcers occurred most frequently along the lesser curvature (HH 43; fig. 1), support the clinical observations that gastric ulcer occurs generally along the lesser curvature (Magenstrasse). If the formation of ulcer were the result of mechanical injury of the mucosa by the motor activity of the stomach and impingement of food against the lesser curvature, the incidence of ulceration following extirpation of the lesser curvature should have been as high as that following extirpation of the greater curvature. The fact that no ulcers occurred in the dogs subjected to the former procedure and that ulcers and erosions developed in 63.6 per cent of the group on which the latter operation was performed suggests that susceptibility of the tissue of the original lesser curvature predisposed to ulceration. On the basis of experiments 1 and 2, in which acute ulcers were obtained in 27 per cent of the dogs after feeding of 1 per cent hydrochloric acid or stimulation with histamine, one is justified in inferring that gastric acidity is a probable factor in the etiology of peptic ulceration. As these were normal animals, the high incidence of ulceration is even more noteworthy, in spite of the fact that the degree of acidity obtained is probably higher than ever occurs in normal human beings. In the human patient with ulcer, however, there exists an ulcer diathesis, in that the patient's predisposition to ulceration is inherent, and his gastric and duodenal mucosa is probably abnormally sensitive to the digestive action of acid gastric juice. The abnormal sensitivity of mucosa to peptic ulceration was

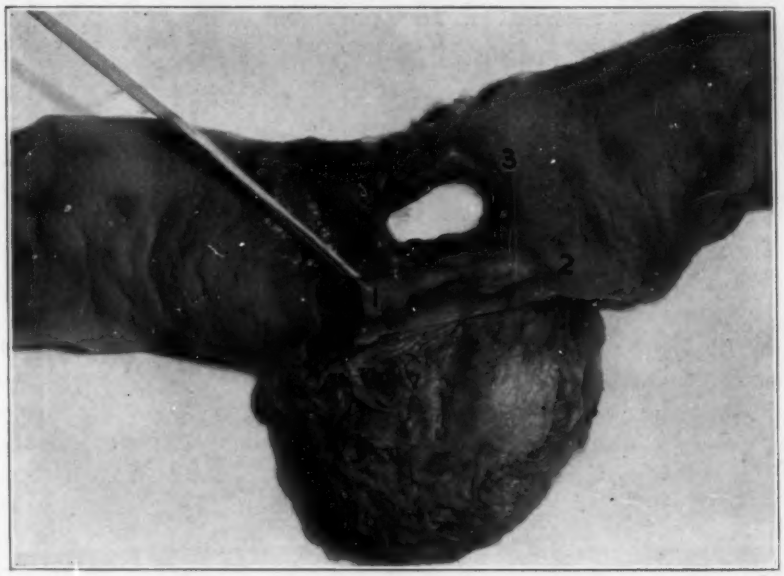

Fig. 8 (dog HH 83).—Histamine was injected three times daily on alternate days over a period of twenty-seven days. The probe passed through the stoma of the gastrojejunal anastomosis into the gastric pouch. There are three jejunal ulcers (*1*, *2* and *3*). Ulcer *3* had perforated into the general peritoneal cavity. Careful microscopic studies reveal that none of these ulcers are marginal, all being located strictly in the jejunum proper.

Fig. 9 (dog HH 88).—Control animal observed for one hundred and fifty-two days. Two chronic jejunal ulcers are present (*A* and *B*). The base of each is filled with granulation tissue and shows evidence of healing along the edges. The arrow points to a loose silk thread hanging into the lumen, which has not caused any ulceration.

illustrated in experiment 2, in which extirpations of the lesser and the greater curvature were performed. As mentioned earlier, the incidence of ulceration was considerably higher (63.6 per cent) in the animals with the greater curvature removed than it was (0 per cent) in those in which the lesser curvature was removed. The acid secretion is primarily from the greater curvature and fundus of the stomach, which is generally accepted, and it would seem probable that if acidity were the only factor the incidence of ulceration should be higher in the animals with the greater curvature present. As the reverse was present, however, it is evident that susceptibility of the tissue is an important factor in the causation of peptic ulcer.

Much has been written, based on clinical and experimental data, in favor of the view that the use of nonabsorbable suture material in gastro-intestinal anastomosis may be of etiologic importance in the causation of ulceration. It is customary not to use silk thread or other nonabsorbable suture material for the hemostatic suture on the mucosa. In spite of the fact that black silk was used only for the seromuscular suture and no. 00 chromic catgut was used for the hemostatic suture in all our experiments, at necropsy loose silk threads were found hanging in the lumen of the main portion of the stomach, or in the stoma of the gastrojejunostomy or of the cholecystogastrostomy (6 animals). The silk thread must have produced at least some irritation of the mucosa in a mechanical way at its point of emergence, but in no instance was an ulceration produced by the thread in our animals (figs. 9 and 10). In 1 dog the silk thread used for the Lembert suture was found at necropsy hanging loose in the stoma of the cholecystogastrostomy and heavily encrusted with bile salts. Yet there was no ulceration. Although silk threads have been found associated with ulcers of the stomach in some of the cases reported in the literature, it is questionable whether they play an important rôle in the production of peptic ulceration in man.

Jejunal Ulceration.—The importance of mucosal susceptibility and hyperacidity in the production of peptic ulcer was illustrated by the results obtained in experiments 3 and 4. In experiment 3 a gastric pouch was formed from either the greater or the lesser curvature and anastomosed to the jejunum. Of 6 dogs in which a pouch of the greater curvature was formed and anastomosed to the jejunum, ulcers developed in all (100 per cent) whether the animal received injections of histamine (3 dogs) or not (3 dogs). In this experiment the condition simulated Meckel's diverticulum containing gastric mucosa, in which the incidence of peptic ulcer of the diverticular mucosa is high. Of 7 animals in which a pouch of the lesser curvature was made and anastomosed to the jejunum, ulcers developed in 5 (71 per cent). The explanation for the ulceration in these animals is that the jejunal mucosa, not being

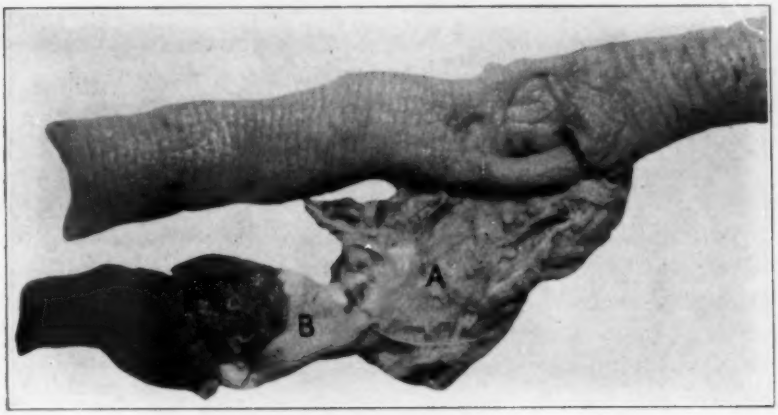

Fig. 10 (dog HH 76).—Histamine was injected three times daily on alternate days over a period of one hundred and twenty-seven days. A chronic callous jejunal ulcer had formed opposite the anastomosis between the gastric pouch and jejunal loop. Note that there is no relationship between this ulcer and the silk thread hanging into the lumen. *A* indicates the gastric pouch and *B*, the gall-bladder to which a piece of liver is attached.

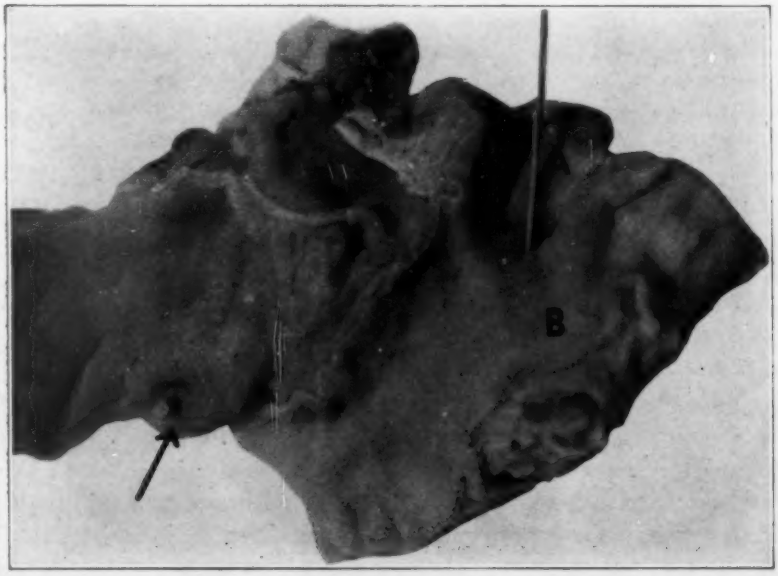

Fig. 11 (dog HH 113).—A control animal observed for ten days postoperatively. The probe is inserted into a perforated marginal ulcer between the gastric pouch *A* and the jejunum *B*. The arrow points to a chronic duodenal ulcer.

accustomed to receive acid gastric chyme and not possessing sufficient inherent resistance to withstand the action of the gastric juice, is digested, with the resultant development of a chronic ulcer. In these experiments the susceptibility of the tissue to ulceration was demonstrated. Of the 7 dogs in which the pouch of the lesser curvature was anastomosed to the jejunum, 3 were given injections of histamine, and ulcers developed in all (100 per cent). Of 4 control animals not receiving histamine, ulcers developed in only 2 (50 per cent). The results obtained in these dogs with pouches of the lesser curvature illustrate the rôle which acidity plays in the production of ulceration, since of the animals receiving histamine ulcers developed in all (100 per cent), whereas of the control group in which histamine was not used ulcers developed in only 50 per cent. The significance of acidity in the development of ulceration was also demonstrated in experiment 3, in which the pouch from the greater or the lesser curvature of the stomach was anastomosed to the jejunum, as follows: In all the 6 animals in which the pouch of the greater curvature was anastomosed to the jejunum ulcers developed, whereas ulcers developed in 5 (71 per cent) of the 7 animals in which the pouch of the lesser curvature was anastomosed to the jejunum. In both of these groups the sensitivity of the jejunal mucosa is presumably the same, the difference in the incidence of ulcers probably being due to the relatively higher acidity in the animals with anastomosis of the pouch of the greater curvature. As mentioned earlier, the gastric acidity is derived largely from the fundus and greater curvature of the stomach, so that the secretion from the pouch of the greater curvature should be greater, with higher values for acid, than that from the pouch of the lesser curvature.

The importance of the neutralization of acidity in the protection of the intestinal mucosa from the digestive action of gastric juice is illustrated by the results obtained in experiment 4, in which pouches from the greater and the lesser curvature of the stomach were anastomosed to the jejunum and the gallbladder. In this experiment the same conditions prevailed as in experiment 3, with the exception that alkaline bile was introduced into the pouch by anastomosing the gallbladder and ligating the common duct. The protective influence of the alkaline bile was demonstrated by the fact that of the 6 animals in which the pouch of the lesser curvature was used ulcers developed in only 3 (50 per cent), as contrasted with the 71 per cent incidence of ulcers in the dogs with a pouch of the lesser curvature in experiment 3, in which the alkaline bile was not present. Of the 7 animals in experiment 4 in which the pouch of the greater curvature was anastomosed to the jejunum and gallbladder, ulcers developed in only 2 (28 per cent), as contrasted with the 100 per cent incidence of ulcers in the animals with a pouch of the

greater curvature in experiment 3, in which the bile was not present. The relatively greater protection in the animals with a pouch of the greater curvature in experiments 3 and 4 when bile was present was probably due to the greater neutralization of a previously higher acidity. The relative protective influence of bile in the pouch of the animals with a lesser curvature was comparatively less than in the animals with a pouch of the greater curvature, probably because in the former the acidity was not so high, so that the neutralization played a less important rôle. The fact that ulcers developed in 50 per cent of the animals with a pouch of the lesser curvature and anastomoses to the jejunum and gallbladder, as compared with 28 per cent of a similar series in which the pouch of the greater curvature was used is interesting. The higher incidence in the former group may have been due to the increased secretion, the result of intact nerve supply.

From our clinical observations [58] and the results obtained in the present investigation, we are of the opinion that there are three factors operative in the production of peptic ulcer: (1) predisposition (ulcer diathesis), which is inherent in certain persons; (2) susceptibility of the tissue and (3) hyperacidity. In the experimental animal ulcer diathesis is known not to occur because ulcers are rarely found in dogs, so that the present investigation was concerned chiefly with susceptibility of the tissue and hyperacidity. As shown in the experiments with extirpation of the gastric curvatures, the lesser curvature of the stomach is more susceptible to ulceration than are other portions. Similarly, anastomoses between the pouches of the curvatures and the jejunum, with the high incidence of ulceration in the jejunum, demonstrate the susceptibility of the jejunal mucosa to peptic ulceration. The rôle of acidity was illustrated in the present investigation (1) by the development of ulcers in normal animals receiving either hydrochloric acid by mouth or injections of histamine, (2) by the high incidence of ulcers of the jejunum when the pouches of the lesser and greater curvatures were anastomosed to the jejunum, and (3) by the relatively lower incidence of jejunal ulcer when neutralization of the acid gastric chyme by bile was accomplished in those animals with anastomoses to the gallbladder.

SUMMARY

An investigation to determine the rôle of tissue susceptibility and hyperacidity in the formation of ulcers is reported. A total of 125 dogs was used, but only 56 animals survived sufficiently long to provide adequate observations.

58. In a subsequent article the clinical application of the experimental findings is to be reported.

In the first experiment hydrochloric acid was administered by mouth or histamine was injected subcutaneously. Erosions or ulcers developed in 27 per cent of the animals.

In the second experiment, either the lesser or the greater curvature of the stomach was extirpated. Of the animals in which the greater curvature was removed, leaving the lesser curvature in situ, ulcers developed in 63.6 per cent, as contrasted with the group in which the lesser curvature was removed, leaving the greater curvature in situ, in which ulcers did not develop. This presumably was due to the greater susceptibility of the lesser curvature of the stomach to the acid gastric chyme.

In the third experiment, a gastric pouch was made from the lesser or the greater curvature and anastomosed to the jejunum. Of the animals in which a pouch was formed of the lesser curvature jejunal ulcers developed in 71 per cent, whereas of those in which a pouch was formed of the greater curvature ulcers developed in 100 per cent. The high incidence of ulceration in this group was undoubtedly due to the susceptibility of the tissue of the jejunum to the acid gastric chyme.

In the fourth experiment, a gastric pouch was made from the greater or the lesser curvature of the stomach and anastomosed to the jejunum and gallbladder. The incidence of jejunal ulcers was 50 per cent in dogs with a pouch of the lesser curvature and 28 per cent in those with a pouch of the greater curvature. The reduction in acidity in this group was undoubtedly responsible for the decreased incidence of ulcers as compared with that in experiment 3, in which there was absence of bile.

On the basis of our clinical observations and the results obtained in the present investigation, we believe that the factors responsible for the production and persistence of peptic ulcer are as follows: (1) predisposition to ulcer (ulcer diathesis), (2) susceptibility of the tissue and (3) hyperacidity. The therapy in cases of peptic ulcer should consist largely of minimizing susceptibility of the tissue by not performing gastro-enterostomy on patients with normal acidity or hyperacidity, and by using those measures which will decrease gastric acidity.

THE ACETABULAR INDEX IN INFANTS IN RELATION TO CONGENITAL DISLOCATION OF THE HIP

SAMUEL KLEINBERG, M.D.
AND
HERMAN S. LIEBERMAN, M.D.
NEW YORK

It is axiomatic that prevention is more valuable than cure. The practice of this principle is nowhere more desirable than in the management of congenital dislocation of the hip. This common lesion has been studied carefully for decades by hundreds of surgeons all over the world with the result that its pathologic process is thoroughly appreciated, and success in its treatment is readily obtainable, yet there is no one established system but a diversity of methods, even when the treatment is applied during infancy. When the condition continues to childhood or early adolescence, not to speak of adult life, without recognition or adequate treatment, then treatment by any method aims only for improvement in ambulation and for some measure of stability of the hip. So it was like a refreshing breeze on a hot summer day to listen to Dr. Putti, in July 1929 in London, expounding his theory of the possibility of recognizing potential dislocation of the hip during the early months of life and of the ease with which the normal relationship of the osseous elements of the hip can be established and assured.

The recognition during the early months of life of the existence of maldevelopment in the structures of the hip, especially the bony parts, likely to eventuate in a dislocation, depends on the appreciation of the differences between the normal and the abnormal roentgenographic appearance of this joint. It has been abundantly emphasized that in congenital dislocations there is, in addition to a poorly developed or anteverted femoral head and neck, a shallow acetabulum, with the roof, or iliac segment, abnormally oblique or even nearly vertical, giving diminished or no resistance to upward displacement of the femur. It occurred to one of us (S. K.) in an examination of a large number of new-born infants, that it might be possible, by study of the angle of inclination of the iliac segment (roof) of the acetabulum with the horizontal line in normal and in congenitally dislocated hips, to arrive at some practical basis of measurement which would help to determine, in the new-born whether the hips are normal or are likely to become dislocated. As the obliquity of the acetabular roof is always marked

in dislocated hips and is regularly slight in normal hips, we concluded that the angle of inclination of the acetabular roof with the horizontal line would be the most serviceable means of judging the normality or abnormality of a hip joint relative to a possible appearance of a dislocation. This angle we shall call, for purposes of convenience, the acetabular index. We have investigated the acetabular index of hips in normal children at birth and at about 2 years of age and in those with congenital dislocations and herein present the results of our study and the conclusions drawn from them.

Twenty-three normal infants, varying in age from 1 to 7 days, were examined and roentgenograms were made of their pelves. Table 1 gives our observations. The acetabular angle, or index, varied between 25 and 32 degrees, the average being 27.5. There was no appreciable difference in the indexes of the right and left hips, nor was there any marked disparity in the indexes of the two sexes. Figure 1 is a tracing of the roentgenogram of the hips of one of these infants, with an acetabular index of 25 degrees.

As most of the infants with congenital dislocation in this country come under observation when they are between 1½ and 2 years old, we next studied the hips of a group of twenty normal children varying in age between 11 and 24 months. Table 2 shows that the average acetabular index in these forty hips was 20 degrees, considerably lower than that in the new-born infants. Figure 2 is a tracing of the hips of a child in this group. The method of mensuration is obvious. A horizontal line is drawn between the triradiate cartilages. A line is then drawn from the upper pole of the acetabulum to the point of contact of the iliac segment of the acetabulum with the triradiate cartilage, forming an angle with the horizontal line. The resultant angle, or acetabular index, reveals the relative depth of the socket of this hip joint and is an index of the resistance which the iliac portion of the acetabulum would present to luxation of the head of the femur. We appreciate that there are many additional factors, such as the thickness of the cotyloid ligament, the conformation and distribution of the capsule of the hip, the size and shape of the head of the femur, the degree of torsion in the neck of the femur and so forth, which influence the development of a dislocation. But the angle of the roof of the acetabulum with the horizontal line, that is, the acetabular index, affords a ready and, we believe, a reliable means of visualizing the future osseous structure of the acetabulum in relation to the head of the femur and aids in deciding whether a dislocation will or will not occur. A high acetabular index warns that a dislocation will or may appear and offers the opportunity of instituting preventive measures, which, from Putti's reports, are eminently successful.

TABLE 1.—*Acetabular Indexes for New-Born Infants* *

Patient No.	Sex	Acetabular Index, Degrees	
		Right Hip	Left Hip
1	M	32	30
2	F	31	30
3	F	28	30
4	M	29	30
5	M	27	25
6	F	30	32
7	F	25	25
8	M	26	25
9	F	25	27
10	F	30	29
11	F	28	28
12	M	27	27
13	M	28	28
14	F	27	28
15	M	25	27
16	F	25	25
17	M	25	25
18	M	25	27
19	F	28	28
20	M	26	27
21	F	26	27
22	F	27	28
23	M	28	30

Résumé

Sex	Acetabular Index, Degrees	
	Right Hip	Left Hip
12 F	27	28
11 M	27	27

	Acetabular Index, Degrees
Average	27.5
Lowest angle	25
Highest angle	32

* These infants were examined in the maternity ward of the Israel Zion Hospital, Brooklyn.

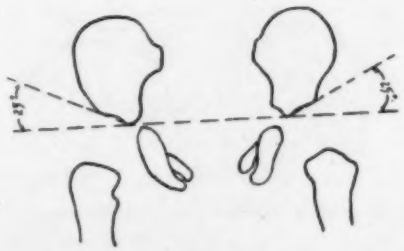

Fig. 1.—The hips of a normal infant at birth.

We next examined the roentgenograms of thirty-five congenitally dislocated hips in children from 12 to 36 months of age. All these children had been treated at the Hospital for Joint Diseases. The average acetabular index was 37.5 degrees (table 3), as compared with an average of 20 degrees for normal children of the same age (table 2) and 27.5 degrees for the new-born (table 1). The difference in the acetabular indexes of normal and congenitally dislocated hips is striking and is graphically represented in figure 3, which is a tracing of the pelvis of a patient in this group (patient 8) who had a congenital

TABLE 2.—*Acetabular Indexes of Normal Hips in Early Childhood*

Patient No.	Age in Months	Acetabular Index, Degrees	
		Right Hip	Left Hip
1	24	21	21
2	24	19	22
3	21	22	22
4	17	21	21
5	16	20	22
6	24	19	19
7	24	19	19
8	24	18	18
9	23	22	20
10	20	19	20
11	24	18	18
12	24	18	18
13	12	21	20
14	20	23	24
15	12	20	20
16	12	20	21
17	11	18	20
18	24	19	20
19	19	25	24
20	18	22	22

Résumé

Total number of normal hips	40
Average age	19 mo.
Youngest	11 mo.
Oldest	24 mo.

	Acetabular Index, Degrees
Average	20
Lowest angle	18
Highest angle	25

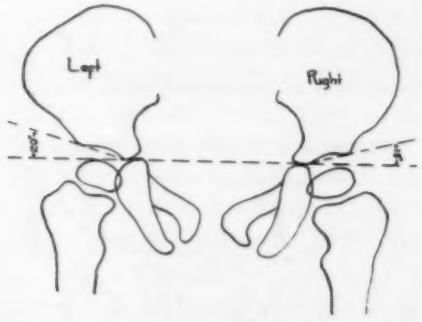

Fig. 2.—The hips of a normal infant at the age of 17 months.

dislocation of the left hip. The acetabular index of the left hip was 38 degrees, while that of the right, or normal hip, was only 22 degrees.

Putti, in describing a method of roentgenologic examination of infants in what he called the preslipping state, classified hips into those with horizontal, obtuse or right angles, depending on the general inclination of the superior, or iliac, segment of the acetabulum. In our investigation we sought more accurate information aiming to establish, if possible, a constant for the normal infant and thus to be enabled more readily to diagnose the abnormal. From our study we can state that an acetabular index above 30 degrees foreshadows a possible dislocation of the hip.

TABLE 3.—*Acetabular Indexes of Congenital Dislocated Hips in Early Childhood*

Patient No.	Age in Months	Acetabular Index, Degrees	
		Right Hip	Left Hip
1	24	42*	20
2	22	45*	30*
3	16	20	40*
4	36	20	38*
5	36	20	42*
6	16	25	40*
7	14	46*	40*
8	18	22	38*
9	12	34*	25
10	36	34*	38*
11	16	18	28*
12	18	20	53*
13	36	20	41*
14	20	18	48*
15	30	39*	48*
16	19	40*	49*
17	21	32*	38*
18	18	25	35*
19	20	40*	24
20	21	33*	39*
21	24	35*	38*
22	27	30*	28*
23	24	28*	29*
24	18	35*	20
25	18	20	28*

Résumé

Total number of congenital dislocated hips	35
Average age	22 mo.
Youngest	12 mo.
Oldest	36 mo.

	Acetabular Index, Degrees
14 Right hips	37
21 Left hips	38
35 Combined hips	37.5

* Dislocated hip.

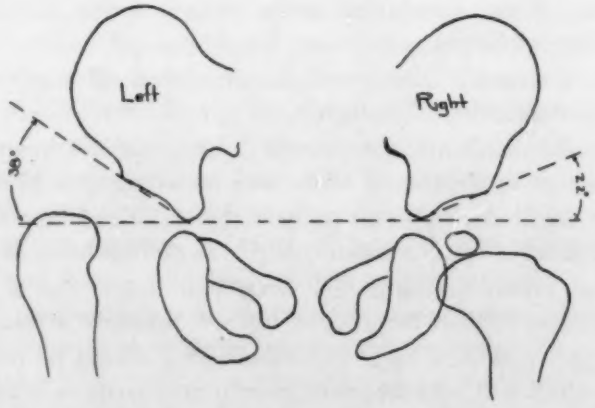

Fig. 3.—Congenital dislocation of the left hip in an infant of 18 months.

In the matter of the technic of roentgenologic examination of the pelvis it is imperative to observe several important details. The infant should be placed on its back, with the lower limbs in contact and in complete extension at the hip joints, with the patellae facing forward. The roentgen tube must be focused or centered in the midline of the body and directly over the superior border of the symphysis pubis. Deviation from this routine, such as tilting of the pelvis or angulation of the tube, will give distorted views and erroneous measurements. In figure 4 there are tracings of two views of the same pelvis. The position of the pelvis in *A* is correct. In *B* the pelvis is rotated to the right and flexed, with a resultant apparent increase in the right and decrease in the left acetabular index and narrowing of the left triradiate space. Reliable information is obviously dependent on accurate roentgenographic technic.

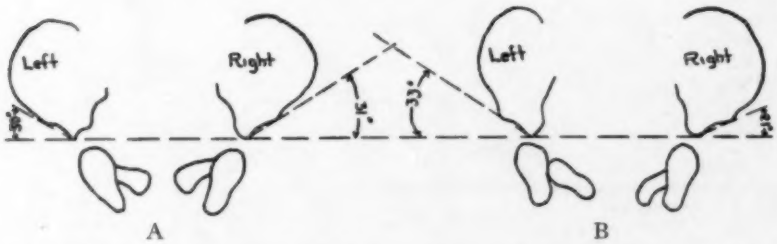

Fig. 4.—Correct and incorrect views of the same pelvis. *A* is taken from the correct angle. In *B* the pelvis is tilted to the right, resulting in a change in the acetabular index and yielding incorrect information.

CONCLUSIONS

1. The acetabular index is the angle formed between the roof or iliac portion of the acetabulum and a horizontal line passing through the triradiate cartilages.

2. The acetabular index in new-born normal infants is regularly low, the average being 27.5 degrees.

3. The acetabular index in normal children about 2 years of age is lower than that in children at birth, with an average of 20 degrees.

4. The acetabular index in congenitally dislocated hips of children of about 2 years of age is constantly high, the average being 37.5 degrees.

5. In an infant having a high acetabular index, that is, above 30 degrees, a dislocation of the affected hip will probably develop.

6. An infant with a high acetabular index should be placed in an apparatus which will hold the lower limbs continuously in marked abduction until the acetabulum and the capital epiphysis have become thoroughly adapted to each other and there is clinical evidence giving reasonable stability.

PATHOGENESIS OF WHITE BILE

HANS G. ARONSOHN, M.D.
CHICAGO

The character of the bile which is obtained at operation for obstruction of the common bile duct varies greatly. The most characteristic bile obtained is thick and dark green, but occasionally there is found so-called white bile. The type of bile obtained in each instance has prognostic as well as diagnostic significance. The important and fundamental problem related to the diagnosis is to determine the conditions that are responsible for the production of the different types of bile on different occasions. From the standpoint of the prognosis it is of vital importance to determine whether or not the liver is functioning normally when white bile is obtained. That this is still an unsolved problem is apparent when one reads the varying opinions expressed in the German and in the American literature concerning the prognosis. The German writers consider that the prognosis is much more serious when white bile is present. The extent of damage to the liver must be known when white bile is being produced, in order to determine whether or not one may expect the organ to function normally after relief of the obstruction.

The literature on white bile is extensive and is especially confusing owing to the fact that authors vary in their conceptions of white bile. In the present discussion I shall exclude the colorless fluid that is found only in the gallbladder. Likewise, I shall not consider the real white bile that is found in cases in which the hepatic cells during the course of their development were never able to produce bile pigment and from the very beginning secreted a colorless fluid. This condition is possible only in the new-born and is so rare that it need not be included here. This paper will be restricted to a discussion of the white bile that is obtained at operation for obstruction of the common duct. In this regard the white bile that is of special interest to the surgeon may be defined as the colorless fluid that is found in the bile ducts and gallbladder and that is free from all bile constituents except a mucin-like protein. The white bile that is found in cases of certain types of intoxication of the liver, such as phosphorus poisoning, will not be considered here.

From the Department of Surgery, the University of Chicago.
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The first definite description of white bile was given in the works of Courvoisier,[1] in 1890. This author emphasized the importance of the colorless fluid found throughout the entire biliary system rather than that found only in the gallbladder.

Kausch [2] and later Quincke and Hoppe-Seyler [3] attacked this problem from the mechanical point of view. They postulated the so-called *Paracholie* theory, which is, in effect, that the hepatic cells because of excess pressure in the bile ducts direct the bile into the blood stream rather than into the bile ducts.

There followed a series of clinical contributions by various authors (Berg,[4] Kehr [5] and others) who described white bile in connection with their studies on cholelithiasis. The chief contribution made by these authors was their review of the most common causes of obstruction in connection with the appearance of white bile, i. e., tumor, especially carcinoma near Vater's papilla, cholelithiasis, stenosis of the common or hepatic duct, spasm of the sphincter and other conditions.

In contrast with these mechanical theories, there arose the idea that functional secretory processes are responsible for the production of white bile in the bile ducts. In accordance with this view Berg expressed the opinion in 1916 that one may consider hydrops of the bile ducts to be a purely functional disturbance, which can be increased by obstruction of the large bile ducts but which is not exclusively produced by it. In addition, Berg mentioned a special congenital affinity of certain parts of the bile ducts for mucostase, which facilitates the production of white bile. This secretory theory introduced a new idea into the consideration of the production of white bile, which predominated for a long time. Even that explanation was not in accord with many clinical observations, however. Pallin,[6] in his work entitled "Cancer in Ductus Hepatico-choledochus," stated: "If one asks why this phenomenon is found only exceptionally, apparently without any rule, one must admit that one does not know anything about it."

Further consideration of the functional secretory theory is found in the works of Rous and McMaster [7] published in 1921. These authors

1. Courvoisier, L.: Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890.

2. Kausch, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:104, 1904-1905.

3. Quincke and Hoppe-Seyler: Die Krankheiten der Leber, in Nothnagel, C. W. H.: Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1899, vol. 18a.

4. Berg, J.: Studien über die Funktion der Gallenwege unter normalen und gewissen abnormen Verhältnissen, Acta chir. Scandinav., supp. 2, 1922, p. 1.

5. Kehr: Ergebn. d. inn. Med. u. Kinderh. **13**:198, 1914.

6. Pallin, G.: Cancer in Ductus Hepatico-choledochus, Lund, Håkan Ohlssons Boktryckeri, 1919.

7. Rous, Peyton, and McMaster, Philip D.: The Concentrating Activity of the Gallbladder, J. Exper. Med. **34**:47, 1921; Physiological Causes for the Varied Character of Stasis Bile, ibid. **34**:75, 1921.

for the first time produced white bile in the experimental animal. As a result of their experiments, which were performed on dogs, monkeys and cats, they stated as their conclusion that the gallbladder concentrates and thickens the bile while the ducts exert an opposite influence, diluting it slightly with a thin secretion of their own. This secretion is colorless and devoid of cholates; in the dog it is almost watery and clear. In an obstructed duct that is separated from the gallbladder or connected with a pathologically changed one such fluid gradually replaces the small amount of bile originally pent up. This is the so-called white bile found by surgeons. In this connection Rous and McMaster distinguished two different systems. In their "white system" the gallbladder is separated from the ducts, and ligation of the common duct results in the production of white bile. In their "green system" the gallbladder maintains its connection with the ducts, and ligation of the common duct results in the production of thickened green bile. These authors found that white bile normally appeared in the white system after nine or ten days, while the longest period of observation on the green system was forty-four days. In their discussion infection was considered as merely incidental, the chief emphasis being placed on the opposite functions of the gallbladder and the bile ducts.

The theory of Rous and McMaster, which seemed creditable enough at the time of its formulation, was weakened by further observations. Berg, in his monograph on the biliary system, expressed the opinion that the underlying cause in the production of white bile is other than obstruction, since obstruction alone in most cases results in the appearance of dark, concentrated bile.

The clinical information on white bile was enriched in 1923 by Judd,[8] who found white bile in nineteen of six hundred and forty-nine cases in which operation was performed on the common or hepatic duct at the Mayo Clinic. One of these cases, in which the bile changed to green immediately after removal of a stone from the common duct, is of special interest with regard to the problem of hepatic function and its relation to the production of white bile.

Clinical observations on relief of obstruction in man led to the experimental work of McMaster, Broun and Rous[9] on the character of the bile secreted after relief of obstruction in dogs. Their method was to insert a drainage tube into the common duct and keep it

8. Judd, E. S., and Lyons, J. H.: White Bile in the Common Duct, Ann. Surg. **77**:281, 1923.

9. McMaster, Philip D.; Broun, G. O., and Rous, Peyton: Studies on the Total Bile: I. The Effects of Operation, Exercise, Hot Weather, Relief of Obstruction, Intercurrent Disease, and Other Normal and Pathologic Influences, J. Exper. Med. **37**:395, 1923; III. On the Bile Changes Caused by a Pressure Obstacle to Secretion and on Hydrohepatosis, ibid. **37**:685, 1923.

clamped for twenty-four hours. The result was a copious secretion of bile with a low pigment content. In another series of similar experiments they produced a colorless fluid by putting a rubber bag into the abdominal cavity of the dog and connecting it with the common duct. The bag was emptied every twenty-four hours through an opening in the abdominal wall.

Further clinical information on relief of obstruction was added in 1930 by Walters and Greene,[10] who described four cases in which white bile was replaced by green bile after relief of an obstruction. These authors suggested that cholangeitis may be of importance in the production of white bile.

The idea that infection may play a part in the production of white bile has been advanced by many authors. Among the first to give this thought serious consideration were Kümmel and Gundermann.[11] Melchior [12] stressed the virulence of the bacteria as a factor in the production of colorless fluid in the ducts. In the Japanese literature Soejima [13] stated that infection is important in the genesis of white bile. Following this idea is the work of Bernhard,[14] who performed a great number of experiments on rats and rabbits and gave due emphasis to the problem of infection. He devised a method of keeping the animals alive long enough for the bile to finish its process of decolorization. By means of continuous injections of sucrose he prevented the death of the animals, which ordinarily occurred from insufficiency of the liver a short time after ligation of the common duct. In rats white bile was found from twenty-four to forty-four days after ligation. As a result of his first series of experiments Bernhard concluded that infection does not play an important rôle in the decolorization of bile. Further experimentation, however, led him to reverse his opinion. By ligation of the common duct in rats he obtained white bile in some instances and green bile in others. Observation showed that the rats from which the white bile was obtained had been afflicted with severe enteritis previous to the operation, while the others were normally healthy animals. On the basis of this observation he stated as his conclusion that infection may play some part, the bacteria traveling

10. Walters, W.; Greene, C. H., and Frederickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, Ann. Surg. **91**:686, 1930.

11. Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:353, 1926.

12. Melchior, E.: Zentralbl. f. Chir. **58**:135, 1931; Beitr. z. klin. Chir. **139**: 162, 1927.

13. Soejima, R.: Ueber die weisse Galle und den Hydrops der gesamten Gallenwege, mit besonderer Berücksichtigung ihrer Aetiologie, Zentralbl. f. Chir. **31**:1738, 1925.

14. Bernhard, F.: Deutsche Ztschr. f. Chir. **222**:66, 1930; Zentralbl. f. Chir. **57**:194, 1930; Beitr. z. klin. Chir. **150**:82, 1930; **154**:389, 1932.

through the intestinal wall and by way of the portal vein into the stagnant bile. Further experimentation on rats in which intestinal infection was produced by means of a special diet of milk or such drugs as sodium bicarbonate or castor oil seemed to verify this idea.

My own work[15] in relation to this problem showed further the importance of infection of the stagnant bile. In my experiments I used rabbits, which by special treatment can be kept alive long enough. The biliary system of this animal is especially sensitive, and changes in the bile occur rapidly.

Briefly, the results of my experiments were as follows: Ligation of the common duct in seventeen rabbits was followed by the production of white bile in four instances. In those four cases only one sample of bile was found to be sterile, the others containing Bacillus coli and streptococci. Seven days after ligation was the shortest time in which white bile occurred. The liver showed little cholangeitic reaction. A striking fact was that in cases in which white bile was collected the hepatic cells showed relatively little changes, whereas in cases in which green bile was found the liver showed extensive necrosis and cirrhosis and contained almost no functioning parenchyma.

As regards infection, I could formulate only a reserved opinion, as my observations were based only on the bacteriologic and leukocytic content of the white bile. Moreover, the bacteriologic results were not certain, since the animals died spontaneously and the bile could be examined only at a later date, leaving open the possibility of a postmortem invasion by bacteria. I concluded from my experiments that infection may play a rôle in the pathogenesis of white bile in rabbits and that, in addition, the condition of the hepatic cells may play some part, since I found a correlation between white bile and a well functioning liver, on the one hand, and green bile with an extremely damaged liver, on the other.

This brief review of the literature shows that the problem of white bile is not yet solved. The mechanical theory of Quincke and Kausch was soon replaced by the idea of a functional secretory process. The white and green systems of Rous and McMaster, however, could apply only to experiments on animals in which no infection occurred. The authors themselves stated that they focused their attention mainly on the cases in which there was no infection. Rous in one of his discussions stated:

> In a dog from which we were making day to day collections of the bile from different portions of the liver, infection occurred in one of the duct systems drained by rubber tubes. Almost at once its output became thickly mucinous and prac-

15. Aronsohn, H. G.: Weisse Galle im Tierexperiment und in der Chirurgie, Beitr. z. klin. Chir. **156**:63, 1932.

tically lost its biliary character, being but faintly tinted with bilirubin, whereas the companion bile that served as a control was thin and dark.

These authors considered the occurrence of an infection a complication which made their results unpredictable. "Infection may so change the gall bladder that a white system develops, where a green one is expected."

It is possible that this infection, observed incidentally by Rous and considered an unnecessary complication in his experiments, is actually a vital factor in the pathogenesis of white bile.

Further proof of the dubiousness of Rous' theory is given by the experiments of Bernhard on rats. Since the rat does not have a gallbladder, ligation of the common duct naturally results in the appearance of the white system of Rous and leads one to expect the production of white bile in all such cases. Nevertheless, in thirty such animals Bernhard found white bile only once.

Another fact supporting the idea that infection is the probable cause is that obstruction of the common duct which results in the production of white bile in man is caused most often by a stone, which is accompanied by infection more frequently than is any other cause of obstruction.

One of the chief obstacles in the study of this problem has been the lack of bacteriologic examinations of the white bile.

Aschoff [16] and Gundermann have shown that colorless hydrops of the gallbladder is often produced by infection. One cannot, however, draw a parallel between white bile and colorless hydrops of the gallbladder. In the first place, the function of the mucous membranes of the ducts and that of the mucous membrane of the gallbladder are very different, as Rous has shown. The obstructed gallbladder, moreover, is a system in which only the mucous membrane of the gallbladder can influence the bile, whereas when the bile ducts are obstructed not only the mucous membrane of the ducts but also the hepatic cells may play an important part.

For these reasons one cannot properly draw an analysis between the pathogenesis of white bile and that of colorless hydrops of the gallbladder. Bernhard, as previously mentioned, artificially produced intestinal infection in rats and obtained white bile after ligation of the common duct. This indirect method of producing infection of the biliary system, however, cannot be considered a final proof of the correctness of the theory of infection. My method was to produce infection of stagnant bile in dogs directly by injection of bacteria into the obstructed biliary system.

16. Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Jena, Gustav Fischer, 1909.

EXPERIMENTATION ON ANIMALS

The procedure was as follows: Ligation of the common duct was performed, accompanied in a few cases by a cholecystectomy, to determine whether the biliary system would react differently without a gallbladder. This was followed four weeks later by a second operation, at which bile was aspirated and bacteria were injected into the walls or cavities of the gallbladder and bile ducts. Infection occurred either spontaneously after ligation of the duct or after injection of bacteria. Cultures were made of the aspirated bile. The dogs either died spontaneously or were killed after from four and one-half to five and one-half months. The animals were constantly observed for any signs of infection, special emphasis being placed on the bacteriologic examination of the bile at different stages.

I chose the dog for my experiments, since this animal survives for many months after ligation of the common duct, thus permitting observations to be made for a much longer period than is possible with rabbits and rats. Moreover, a second operation can be performed on dogs with much less risk than on smaller animals.

The operations were performed with the animals under ether anesthesia and with strictly aseptic conditions. Obstruction was produced by double ligation of the common duct and transection between the two ligatures.

In every case great care was taken to determine the presence or absence of an accessory duct. In no instance were the ducts found to be grown together at any time after the operation. The wounds for the most part healed well, with the exception of a few small stitch abscesses.

Various strains of bacteria were used for the injections, Bacillus coli yielding the best results. Staphylococcus aureus and Staphylococcus albus did not produce the desired infection in all cases, while some highly virulent organisms, such as Streptococcus haemolyticus, were fatal to the animal in a short time.

A suspension of the bacteria in saline solution containing about a billion organisms per cubic centimeter was used. Two cubic centimeters of this suspension was injected into the walls and cavities of the bile ducts and gallbladder.

I used the following features as criteria of the presence of infection in my clinical observations: degree of apathy, ability to take nourishment, quality of the stool and the presence and extent of jaundice.

Different parts of the gallbladder and bile ducts were selected for the aspiration whenever possible. A bacteriologic examination of the bile was made in every case, and also a chemical analysis and a sediment test whenever there was sufficient material. The bilirubin content was determined by the method of Schmidt and Jones,[17] the cholesterol content by that of Bloor [18] and the content of bile acids by that of Schmidt and Dart.[19] Histologic examinations were made in every case.

Ligation of the common duct was performed on eleven dogs, with superimposed cholecystectomy in two cases. Four of these dogs, constituting group 1, died from two to twenty days after the first operation. Six of the seven remaining

17. With reference to the bilirubin determinations, it should be stated that there are no strictly accurate methods, but I have used the method of Schmidt and Jones, which I believe to be the most accurate method in use at present (Schmidt, C. R., and Jones, K. K.: A Method for the Determination of the Total Pigment in Bile, Proc. Soc. Exper. Biol. & Med. **34**:17, 1936).

18. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227, 1916.

19. Schmidt, L. W., and Dart, A. E.: Estimations of Bile Acids in the Bile, J. Biol. Chem. **45**:145, 1920.

animals were subjected four weeks later to a second operation, which consisted of aspiration of bile from the gallbladder and injection of bacteria. The seventh animal was used as a control. Group 2 consisted of three dogs which died from one to thirteen days after the second operation. The three other dogs and the control dog, which remained alive and were killed from four and one-half to five and one-half months later, constituted group 3. This last group included the two dogs on which cholecystectomy was performed.

There follow three protocols of dogs in which the character of the bile showed a significant change and the protocol of the control animal. The bile from all the dogs in group 1 and from two members of group 2 was grossly normal with respect to coloration; hence the protocols for those dogs have been omitted. The bacteriologic results for all the specimens, however, are of significance and have been included in table 1.

Dog 415.—The first operation, consisting of ligation of the common duct and cholecystectomy, was performed on June 19. Severe jaundice developed, and the stool was colorless. There were no marked symptoms. The animal recovered in a short time. Persistence of a small stitch abscess was noted.

The second operation was performed on July 17. Extensive adhesions were present, and the common and the hepatic duct were markedly dilated. Aspiration yielded a small amount of dark green bile. Two cubic centimeters of a suspension of Staph. aureus in saline solution was injected into the wall and the cavity of the common duct. A bacterial culture gave negative results. A few leukocytes were observed in the sediment.

The postoperative course was severe; the animal was completely apathetic for twelve days and refused to take food. Signs of recovery were noted after three weeks.

On December 5 the dog was electrocuted. Postmortem examination showed an abscess of the spleen as large as a kernel of rice. Extensive adhesions were noted around the common duct, which was 1 cm. in diameter. The diameter of the cystic duct measured 6 mm. The intestinal mucosa was red and hyperemic. Three cubic centimeters of mucinous, watery, clear fluid was aspirated.

Culture of the bile yielded Str. haemolyticus and Bacillus Welchii. Chemical analysis showed that no bilirubin, cholesterol or bile acids were present. The sediment contained many leukocytes.

In the liver there was marked fatty infiltration, some areas being spared. No pigment was present in the hepatic cells, but a good deal was present in the capillaries. Little interstitial round cell infiltration was seen.

Dog 772.—The first operation, consisting of ligation of the common duct and cholecystectomy, was performed on July 25. Severe jaundice developed, and the stool was colorless. There were no marked symptoms. The animal recovered in five days.

The second operation was performed on August 23. Extensive adhesions were present between the duodenum and the liver. The common duct was in the depth of these adhesions and not greatly dilated. The hepatic duct was only slightly dilated.

Aspiration yielded 0.5 cc. of dark green bile. Two cubic centimeters of a suspension of B. coli in saline solution was injected into the wall and cavity of the common duct. Bacterial culture yielded Staph. albus.

Serious symptoms were noted for several weeks, and the animal remained prone. Jaundice was severe, and the stool was bloody for a few days. Gradual improvement occurred. Five weeks after operation the animal was again in good condition.

On December 10 the animal was electrocuted. Postmortem examination showed that the general condition was good. Jaundice was slight. Extensive adhesions were noted between the liver and the duodenum. The bile ducts were slightly

TABLE 1.—*Results of the Bacteriologic Examination of the Bile*

Group	Dog No.	Duration of Life	First Period, 2 to 20 Days	Second Period, 29 to 41 Days			Third Period, 4½ to 5½ Months	
				4 Weeks After First Operation				
				Bacteria Present	Bacteria Injected	Bacteria Found Post Mortem		
1	789	2 days	Str. haemolyticus, B. coli, B. Welchii					
	990	5 days	Str. haemolyticus, B. Welchii					
	771	11 days	B. coli, B. Welchii					
	886	20 days	Staph. aureus, B. Welchii					
2	792	29 days		Gram-positive rod, B. coli	B. coli	B. coli, streptococcus, gram-positive rod-shaped bacteria		
	768	32 days		Str. haemolyticus	Staph. aureus	Str. haemolyticus, Staph. aureus, B. Welchii	Between white and green bile	
	728	41 days		Sterile	Staph. aureus	Staph. aureus		
							After Electrocution	
							Bacteria	Bile
3	415	5½ mo.		Sterile	Staph. aureus		Str. haemolyticus, B. Welchii	White
	772	4½ mo.		Staph. albus	B. coli		B. coli	White
	789	4½ mo.		Sterile	B. coli		B. coli, diphtheroid bacillus	Almost white
	991 Control	4½ mo.	.....				Staph. albus	Deep green

dilated. A hemorrhagic infarct the size of a walnut was present in the spleen. The intestinal mucosa was red and contained mucus. Aspiration yielded 0.5 cc. of fluid, which was bloody but not bile-colored.

After the bile had been centrifugated the supernatant fluid was clear. Bacterial culture yielded B. coli. Chemical analysis gave negative results for bilirubin. The sediment contained many leukocytes, erythrocytes and amorphous crystals.

Histologic examination of the liver showed marked fatty infiltration, which spared large areas. Pigment was noted in the capillaries but not in the hepatic cells. There was evidence of a little interstitial reaction.

Dog 991.—Ligation of the common duct was performed on August 1. Severe jaundice developed, and the stool was colorless. No marked symptoms were noted.

On December 14 the animal was electrocuted. Postmortem examination showed that the dog was emaciated and severely jaundiced. Adhesions were present between the gallbladder and the duodenum. The gallbladder was distended and the bile ducts were markedly dilated, the common duct being 1.5 cm. and the hepatic duct 1 cm. in diameter. The intestinal mucous membrane showed no changes. Aspiration of the bile duct and the gallbladder yielded large amounts of thick, dark green bile with the consistency and appearance of tar.

The bile was so thick that it had to be mixed with water for chemical analysis, and the results obtained were questionable. Bacterial culture of the bile yielded Staph. albus. Chemical analysis gave the following values: bilirubin, 148 mg.; cholesterol, 118.6 mg., and bile acids, 910.8 mg. per hundred cubic centimeters. The sediment contained many leukocytes, a good deal of pigment and amorphous crystals.

Histologic examination of the liver showed little evidence of interstitial reaction. Fatty degeneration was noted in some areas. Pigment was present in the hepatic cells.

The gallbladder was normal.

Dog 768.—The first operation, ligation of the common duct, was performed on July 5. Severe jaundice developed, and the stool was colorless. The dog was emaciated and preferred to lie prone. Diarrhea occurred. Severe symptoms were noted for three weeks, and then slight recovery followed.

The second operation was performed on August 2. An extreme degree of jaundice was noted, affecting especially the internal organs and the omentum. Ascites was present. The gallbladder and bile ducts were greatly dilated. Aspiration yielded thin, slightly brownish bile. Two cubic centimeters of a suspension of Staph. aureus in saline solution was injected into the wall and cavity of the common duct. Bacterial culture yielded Str. haemolyticus.

The postoperative course was severe, and the animal died on August 6.

Postmortem examination showed evidence of purulent peritonitis. Thin, slightly brownish bile with a grossly diminished color content was aspirated. Bacterial culture of the bile yielded Str. haemolyticus, Staph. aureus and B. Welchii. The sediment contained many leukocytes and erythrocytes. No chemical analysis was made.

RESULTS

White bile was found in all three dogs in group 3. In two of these cases the bile was entirely colorless, while in the third the coloration was so faint that the bile could safely be considered to be white, in accordance with the work of Klose and Wachsmuth,[20] who included under this heading bile that still retained a slight amount of coloration. Only one animal (dog 768) in group 2 showed significant results, the bile from this animal being much lighter in color than normally. It was not so dilute that it could be called white bile, but there was a definite tendency in that direction. Chemical analysis gave results that were in accordance with the colorimetric evaluation. The bile from the dogs in group 3 showed a low content of bile constituents. Bilirubin

20. Klose, H., and Wachsmuth, W.: Arch. f. klin. Chir. **123**:1, 1923.

was absent from the bile of dogs 415 and 772 and had an extremely low value (0.99 mg.) in dog 789. The cholesterol and bile acids either showed very low values or were absent. These results are graphically represented in tables 1 and 2. A study of the results shown in these tables immediately suggests the rôle played by infection.

It would be easy to prove that infection is responsible for the production of white bile in dogs if one could draw a hard line between infection and noninfection. Theoretically, if the infection theory is correct, an animal with white bile should show clinical symptoms of illness during the period of obstruction, and its bile should contain bacteria and many leukocytes. On the other hand, a control animal should not show any clinical signs of infection, and there should be green bile containing no bacteria and leukocytes. From the practical standpoint these limits are not sharply defined, and the conditions for determining the presence of infection can be only partially fulfilled. The fact that bile is sterile after four or five months does not prove that an animal did not undergo a severe infection some time during that period. Bacteria may have been present at one time and may have disappeared before the time of examination. On the other hand, bile may contain bacteria even though there are no clinical signs of infection. Recent extensive investigations by Andrews [21] have proved the correctness of these statements. The significance of the bacteriologic examinations will be more thoroughly disclosed later in the paper.

Although there are no definite single criteria for determining the presence of infection, one can, by using a combination of these signs, judge whether or not there has been infection. Consequently, I used as diagnostic signs for the presence of infection the following criteria: (1) the clinical picture after operation (postoperative condition, course), (2) the bacterial and leukocytic content of the bile obtained four weeks after the operation from the living dog, (3) the bacterial and leukocyte content of the bile post mortem and (4) the histologic picture of the liver.

The members of group 3 showed the following general characteristics in common: an uneventful course after the first operation, aspiration of sterile bile four weeks later (with the exception of dog 772), a severe course after the second operation, a high content of virulent bacteria in the bile post mortem (Str. haemolyticus, B. coli) and a high leukocytic content.

These facts show that these animals suffered no ill effects as a result of the first operation. The fact that Staph. albus was present in the bile of dog 772 is of little significance, since this organism is rela-

21. Andrews, Edmund: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081 (Dec.) 1932.

TABLE 2.—*Results of the Bacteriologic Examination of the Bile of Five Dogs*

Dog No.	First Operation	Post-operative Course	Second Operation, 4 Weeks After First Operation			Post-operative Course	Duration of Life	Bile Obtained Post Mortem					
			Aspirated Bile						Chemical Analysis				
			Color	Results of Culture	Bacteria Injected			Color	Bilirubin, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Bile Acids, Mg. per 100 Cc.	Bacteria	Sediment
415	Ligation of common duct, cholecystectomy	Uneventful	Green	Sterile	Staph. aureus	Very serious	5½ mo.	White	.....	.....	.....	Str. haemolyticus, B. Welchii	Many leukocytes
772	Ligation of common duct, cholecystectomy	Uneventful	Green	Staph. albus	B. coli	Very serious	4½ mo.	White	.....	.....	.....	B. coli	Many leukocytes and erythrocytes
789	Ligation of common duct	Uneventful	Green	Sterile	B. coli	Severe for 6 or 8 days	4½ mo.	Almost white	0.99	1.9	108.86	B. coli, diphtheroid bacillus	Medium number of leukocytes
991 Control	Ligation of common duct	Uneventful	.....	.....	.....	.....	4½ mo.	Green	148.00	118.6	910.80	Staph. albus	Some leukocytes
768	Ligation of common duct	Very serious	Between white and green	Str. haemolyticus	Staph. aureus	Very serious	32 days	Between white and green	.....	.....	.....	Str. haemolyticus, Staph. aureus, B. Welchii	Many leukocytes and erythrocytes

tively avirulent. As a result of the second operation all the clinical and bacteriologic signs of severe infection were noted. On the other hand, the control dog, which was killed four and one-half months after ligation and on which no second operation had been performed, had dark green bile and showed no signs of infection. There was an uneventful postoperative course, and bile obtained post mortem contained only Staph. albus and a few leukocytes. Dog 768 had a serious course following ligation of the common duct, while culture of the aspirated bile showed Str. haemolyticus. The other two members of group 2, however, from which green bile was obtained, showed no clinical symptoms until after the second operation. A consideration of these results leads me to the following conclusion:

Experimentation on dogs shows that white bile is produced in those cases of obstruction of the common duct in which infection is present and extends over a long period.

EXPERIMENTAL AND CLINICAL SIGNIFICANCE OF BACTERIA AND LEUKOCYTES IN THE BILE

In my experiments white bile yielded B. coli in two cases and Str. haemolyticus and B. Welchii in two others. With regard to the clinical cases, which will be reported later, the only sample of bile that was examined bacteriologically contained B. coli and B. Welchii. To evaluate properly the significance of the bacteriologic findings, one must refer to the literature on this subject. Bernhard reported the culture of B. coli in one case, staphylococcus in another and streptococcus in a third, while Melchior obtained B. coli once. On the other hand, Klose and Wachsmuth as well as Gorke [22] and Kausch obtained negative results in three cases in which white bile was found. On the basis of these findings Kausch not only denied the truth of the infection theory but went so far as to say that white bile can be produced only in the absence of infection.

A possible explanation for the negative bacteriologic findings reported in the literature may be that the bacteria at the time of examination were dead. To substantiate this idea, one has only to bear in mind the sequence of events which sometimes occurs in the case of a long-lasting abscess. The abscess in its acute stages may be swarming with micro-organisms yet may become sterile and free from leukocytes after some time. Many cases illustrating this point have been reported in the literature. Jósa [23] stated that the bacteria in an appen-

22. Gorke, H.: Deutsche med. Wchnschr. **48**:1166, 1922.

23. Jósa, Ladislaus: Ueber einen seltenen Fall von Appendicitis phlegmonosa im obliterierten Wurmfortsatz, Zentralbl. f. Chir. **62**:259, 1935.

dix which has become stenosed as a result of inflammation lose their virulence and for the most part die.

By analogy, it is not surprising to find that old white bile is sterile. In my own experiments the bacteriologic examinations gave positive results in all cases even after four and one-half or five and one-half months. Perhaps the mildly virulent nature of the bacteria did not allow the process to complete itself within so short a time. In the only clinical case in which a bacteriologic examination was made the results were positive.

While negative bacteriologic findings do not necessarily speak against the infection theory, positive results form a strong support for it. It must be borne in mind in this connection that the gallbladder, according to the work by Andrews, has a normal bacteriologic flora, consisting of streptococci, members of the B. coli group and B. Welchii. It is evident that no definite conclusions on this subject can be drawn from the bacteriologic findings alone.

Further valuable information about the presence of infection in cases in which white bile is found is given by the leukocyte content, which is greatly increased in the presence of infection.

White bile, in clinical reports, is often referred to as milky bile and is described as a white flaky material mixed with colorless fluid. The French refer to this as *bile laiteuse*, while in the protocols of one of my own clinical cases the colorless fluid is described as milky. Unfortunately, not many microscopic examinations of this material have been made. It is possible that white bile consists, in part at least, of cholesterol. Nevertheless the microscopic diagnoses that have been made indicate that these flakes consist in large part of leukocytes as well. The rôle played by the leukocytes in effecting this decolorization is best illustrated in the extreme but rare condition of purulent cholangeitis in which the green hepatic bile is replaced by a colorless purulent fluid. Probably the most purulent stage had already been passed at the time of examination, thus accounting for the small number of bacteria and leukocytes found.

Thus, in evaluating the pathogenesis of white bile one may say with some assurance that bacteria and leukocytes, if not present at the time of examination, were present at least at some time during the development of the colorless fluid.

There are two possible routes by which bacteria may enter the bile: One is by direct ascension up the ducts, as in infection due to the presence of a calculus; the other is a hematogenous spread from the intestine by way of the portal vein into the biliary system.

CLINICAL CASES

Few clinical cases in which white bile was found have been reported in the literature. It may be of some value to report a few such cases in this regard and to study the pathogenesis of white bile on the basis of the clinical cases available.

Examination of the records of operation on the common bile duct at the University of Chicago Clinics for the last five years reveals that there was only one outspoken case of white bile. There were three other cases in which the bile either was light green or on chemical examination showed so little of the normal bile constituents that I feel justified in considering them in this discussion.

It would be well to mention at this point that my observations were not made on bile collected from the liver in all the cases to be reported. Nevertheless, since drainage of the gallbladder resulted in a collapse of the dilated bile ducts, I feel justified in assuming that the bile aspirated from the gallbladder represented that present throughout the entire liver-gallbladder system.

The obstruction was caused in one case by carcinoma of the head of the pancreas and in another by a stone in the common duct. In two other cases it resulted from old injuries following operations for stones in the common duct.

The prognosis on the basis of these cases is favorable. In view of the fact that one patient died of peritonitis ten days after the operation, the mortality, as far as I can judge from the few cases cited, corresponds fairly well with Judd's figure of 21 per cent.

CASE 1.—Mrs. E. A., aged 35, had a history of pain in the epigastrium and the right upper quadrant of the abdomen beginning twelve years previously. She did not remember whether she had been jaundiced. Seven years before admission the gallbladder, which she said contained stones, was removed, and since that time the patient had had periods of jaundice, chills, tenderness in the epigastric region and itching. Attacks occurred with great irregularity, sometimes lasting for ten days. The present attack had lasted for one week and had consisted of tenderness in the epigastric region, chills, nausea, vomiting, jaundice, itching and a temperature as high as 102 F.

At operation a short bile duct was found anastomosed to the duodenum or stomach in a mass of adhesions. No stones were palpable. It seemed probable that there had been an injury and possible resection of part of the common bile duct followed by anastomosis of the duodenum and the hepatic duct. The bile duct was seen to contain a clear white fluid. Nothing was done at the operation except free the ducts from adhesions. The postoperative course was normal and satisfactory.

This case clearly illustrates the clinical picture seen in cases in which white bile is found. The clinical history revealed that attacks of pain in the right upper quadrant had occurred irregularly for seven years

after cholecystectomy for cholelithiasis. These attacks, lasting as long as ten days, had been accompanied by more or less severe jaundice, fever, chills and tenderness.

In this case there were short recurrent attacks, due to more or less complete obstruction, which disappeared in a few days without treatment. Fever, chills and epigastric tenderness pointed toward an inflammatory process in the biliary system, but the exact nature of this process is not known. It may have been either secondary cholangeitis following primary mechanical obstruction or primary cholangeitis causing obstruction by swelling of the mucous membrane. Which of these processes had taken place is of no consequence for this discussion. The significant point is that the common duct was obstructed at intervals over a long period, with accompanying infection.

On the basis of these facts it was no surprise on operation to find colorless bile. In fact, the shortness of the duration of the attacks as well as the mild nature of the jaundice and infection led me to expect a less completely decolorized bile. The findings at operation explained this discrepancy, since obstruction was found to be more complete anatomically than the clinical symptoms indicated.

CASE 2.—Mrs. I. M., aged 35, for the past four years had had an intermittent dull pain in the right lower quadrant, without any fever, tenderness, nausea, vomiting or jaundice. A roentgenogram revealed stones in the gallbladder.

On Oct. 18, 1929, cholecystectomy was performed. The gallbladder contained numerous greenish stones, but there were no signs of acute infection. A few days later, however, as a result of injury during the operation, the common duct was completely obstructed.

On October 29 the common duct was repaired and a T tube inserted. The postoperative course was uneventful. The biliary discharge was profuse at first. During the next two years, however, the patient had frequent attacks of pain, fever and jaundice.

In January 1931, because of severe pain, profuse diarrhea, jaundice and pruritus, a diagnosis of cholangeitis and obstructive jaundice was made.

On March 19, 1931, the common duct was again repaired and a T tube inserted. Daily specimens of bile were obtained until the tube was withdrawn forty days after operation. For a few days after the operation the flow from the tube was scanty, and the material was light, as one would expect after relief of obstructive jaundice. From then until the tube was withdrawn, however, the bile was of normal appearance. Chemical examination by the aminonitrogen method showed absence of bile salts and an unusually low cholesterol content for nearly three weeks. The values soon rose to fairly normal levels, however.

This case is very similar to the preceding one. Cholecystectomy resulted in such severe injury to the common bile duct that a few days after operation there was complete obstruction, making necessary a second operation. A T tube was inserted, and a profuse bilious discharge appeared. This fistula remained in place for two years, and during that period the patient had frequent attacks of pain in the upper

part of the abdomen, jaundice of varying intensity and fever. During those attacks the flow of bile from the fistula ceased. The stool was clay-colored and the urine dark. The clinical diagnosis was obstructive jaundice and cholangeitis. The last attack, of special severity, lasted for seven weeks and was accompanied with profuse diarrhea, making necessary another operation and the insertion of a T tube. For a few days after the operation the bile issuing from the tube was light-colored, and then it became normal again.

This was a case of biliary stasis accompanied with infection. The individual attacks were of short duration, indicating that the inflammatory process was mild. However, the last attack, which led to operation, was of special severity and of long duration (seven weeks) and was characterized not only by cholangeitis but by profuse diarrhea. It is highly probable that the last obstruction was chiefly responsible for the change in the character of the bile. The bile would probably have been completely discolored if the previous attacks during the last two years had been the result of complete obstruction.

Case 3.—Mr. I. D., aged 73, for the past four years had had attacks of pain in the right upper quadrant of the abdomen, radiating to the right shoulder. Two of the attacks were especially severe and were accompanied with nausea and vomiting, followed by jaundice, which lasted for six weeks. The attacks were all accompanied with chills, fever and tenderness in the right upper quadrant. The last attack was especially severe, occurring from ten to fourteen days before admission and accompanied with pain similar to that previously mentioned, chills, fever and the excretion of dark red urine.

On admission to the hospital the patient had jaundice and pain. At operation a stone was removed from the common duct, and a T tube was inserted. There were adhesions to the gallbladder, which was slightly thickened. The common duct was greatly dilated. There were about twenty-five stones in its lower portion and about thirty-five in its upper portion and in the hepatic ducts.

Daily drainage yielded on the average from 300 to 400 cc. of fairly clear bile. Chemically the specimens for the first four days contained a small amount of cholesterol, but the amount rapidly became normal. Not one of the daily specimens contained any bile salts.

The patient died of biliary peritonitis on the tenth day. At autopsy both the hepatic and the common duct were increased in diameter, and five stones were present in the latter. The liver weighed 1,550 Gm., and the cut surface was somewhat opaque and brownish rather than green. Microscopically there was a considerable increase in the amount of periportal connective tissue, and in some places there was marked round cell infiltration. A diagnosis of beginning biliary cirrhosis was made. Bacteriologic examination of the bile showed B. coli and B. Welchii.

In this case there was a history of severe attacks due to the presence of gallstones for the last four years, two of the attacks being especially severe and indicating the presence of complete obstruction. These attacks were accompanied with vomiting, nausea, fever and chills and were followed by jaundice, lasting as long as six weeks. Operation

revealed a greatly dilated common duct obstructed by stones. A T tube was inserted and the bile collected. The bile was clear and on chemical examination showed an absence of bile salts and a low concentration of cholesterol. After four days, however, the bile became normal. At postmortem examination the bile was seen to contain B. coli and B. Welchii. Grossly the liver was abnormally light green, while microscopically there were areas of round cell infiltration and a tendency toward biliary cirrhosis.

The clinical history as well as the postmortem examination showed all the necessary conditions for the pathogenesis of white bile. There was complete obstruction of the common bile duct, accompanied with an infection of the liver that was so severe as to cause the appearance of beginning biliary cirrhosis. White bile was obtained, as would be expected, but it was not as completely decolorized as the conditions present indicated that it would be. It is possible that the presence of a gallbladder that was fairly normal anatomically operated against the formation of white bile by favoring concentration.

Case 4.—Mr. O. H., aged 69, had been jaundiced, without remissions, for six months, and at the same time severe diarrhea had developed. The stools were colorless, but the diarrhea disappeared after the patient was placed on a special diet, only to reappear two weeks before his admission to the hospital. The patient had lost 50 pounds (22.7 Kg.) in the last year and for the past six weeks had had abdominal distention and edema of the legs. At no time did he have pain. The temperature before operation was 100.5 F.

Operation revealed the presence of carcinoma of the head of the pancreas. The common duct was greatly dilated (3 cm. in diameter) and tense. The gallbladder was greatly distended and contained about 100 cc. of turbid brownish, milky bile. When this material was aspirated from the gallbladder the common duct collapsed. Exploration revealed a patent cystic duct and carcinomatous metastases in the liver. Cholecystogastrostomy was performed, and four days later bile was found in the stool. The patient left the hospital in good condition.

The history of this patient is of particular interest in that biliary stasis was accompanied with intestinal infection. The stasis was caused by a carcinoma of the head of the pancreas, which was responsible also for the complete obstruction of the common duct and the jaundice of six months' duration. The condition was accompanied with severe diarrhea, although there were no symptoms of infection of the biliary system. The extreme dilatation of the bile ducts and gallbladder observed at operation was an anatomical indication of the completeness of the obstruction. The bile that was aspirated from the gallbladder was partially discolored. One may safely assume that the bile from the liver was of the same nature, since puncture of the gallbladder resulted in collapse of the duct system.

The occurrence of intestinal infection with obstruction of the common duct and biliary stasis corresponded to the results obtained by

Bernhard in his experiments on rats. The carcinoma of the head of the pancreas probably was instrumental in the production of diarrhea by way of the pancreatic enzymes. This then resulted in an intestinal infection, which may have caused secondary involvement of the biliary tract and thus probably explains the sequence of events.

In addition to the cases just discussed in which white bile was found, I shall describe two cases in which long-lasting stasis of the bile did not result in decolorization. To illustrate this condition, I have chosen two cases of congenital obstruction, since it is easy in these cases to demonstrate why the bile does not undergo any change.

CASE 5.—R. C., aged 1 month, was seen to have blue spots on the face immediately after birth but was otherwise normal. On his admission to the hospital, four weeks after birth the infant's skin was very dark, the scleras were yellow and the mucous membrane was pigmented. The liver extended 2 fingerbreadths below the costal margin, the urine was dark green and contained bilirubin and the stool was clay-colored. Operation revealed complete obliteration of the common and the hepatic duct. The liver was greatly enlarged and slate black. The gallbladder was thin and somewhat distended and contained clear golden yellow bile. An anastomosis was made between the fundus and the anterior wall of the stomach. Culture of the bile showed no growth. There was no fever, and the postoperative course was excellent.

Immediately after birth there were signs of complete obstruction of the common duct, i. e., clay-colored stool, general severe jaundice, urine containing dark green bile and hemorrhages in the skin of the face. The general condition of the patient, however, was little disturbed, there being no pain or fever, and the intake of food was normal.

Operation, performed thirty days after birth, revealed normally colored bile in the gallbladder and a strikingly dark liver, apparently rich in bile pigments. The finding of green bile in a case of congenital obliteration of the bile ducts of thirty days' duration is not at all surprising. Neither clinically nor anatomically were there any signs of infection accompanying this stasis. This was further substantiated by the sterile bacteriologic cultures.

Since white bile has been seen to be produced after a period of obstruction lasting for sixteen days, an obstruction of thirty days' duration would surely be long enough for white bile to be produced. Besides, this stasis may have been of still longer duration than thirty days, since obliteration of the ducts may have occurred during fetal life.

CASE 6.—I. D., aged 5 months, had become increasingly jaundiced since two days after birth. He had gained weight poorly, the stools had always been white and the urine was deep orange. On admission the infant was intensely icteric, not well developed and poorly nourished but did not appear acutely ill. The liver was greatly enlarged, the urine contained bilirubin and examination of the stool revealed no urobilin.

At operation the liver was observed to be hard and somewhat enlarged, and the gallbladder was very small, containing 2 cc. of clear mucus. An attempt was made to find the hepatic duct by means of an aspirating needle, but without success. The gallbladder was opened, and its cavity was packed with gauze, which was then led to the surface. The infant died one day later of bronchopneumonia.

At autopsy the liver was observed to be hard and green. All lobular markings were obliterated by a diffuse infiltration of whitish tissue. The gallbladder contained no bile, and its mucosa was not bile stained. The cystic duct, common duct and ampulla of Vater were not patent, and the hepatic duct was absent. On section the liver showed a marked growth of fibrous connective tissue in the portal triads but only a few polymorphonuclears and lymphocytes. In this connective tissue and about the periphery of the lobules there was a marked increase in the number of bile ducts, the ducts often containing dark masses of bile pigment. The capsule of the liver was greatly thickened and contained many bile ducts. Many of the capillaries were distended with bile, especially those in the center of a lobule.

This case is very similar to the preceding one, except that at operation thick green bile was found only in the liver, while the gallbladder contained clear mucus.

The clinical picture revealed no signs of infection. While it is true that the infant was poorly developed and poorly nourished, it is specifically stated in the history that he was not acutely ill. The absence of infection, proved anatomically as well as clinically, could account for the finding of thick green bile in the liver. But how can the presence of clear fluid in the gallbladder be explained? If the contents of the gallbladder had originally been green bile, there is no reason to believe that it alone, and not the bile from the liver, should have become discolored. This is readily understood if it is assumed that the hepatic ducts were already obliterated when the liver became functional during fetal life. That would have prevented the gallbladder from ever receiving any bile. The slight amount of mucus present had probably been secreted by the mucous membrane of the gallbladder itself, stimulated by the stasis.

PATHOGENESIS OF WHITE BILE

Closed System.—On the basis of the foregoing evidence one can now offer a likely explanation for the fact that in some cases of obstruction white bile is obtained and in others green bile. White bile is probably produced by an infection of stagnant bile which has existed for a long time.

This point is one of the most important factors in the understanding of the pathogenesis of white bile. One must next attempt to determine the function of infection in the process and, in addition, to explain what white bile is. Does infection have the power to change green into white bile, or is white bile the product of infected bile ducts, after the green bile has been in some manner removed?

Concerning the mechanism of decolorization, I again refer to the studies of Gundermann and Bernhard. The former showed in his studies on hydrops of the gallbladder that decolorization is brought about by the action of leukocytes, which take up the bile pigment and digest it by means of their ferments. Bernhard, in his studies on rats, observed the same phenomena in hepatic bile. In my experimental work I was unable to find bile pigment in leukocytes, and I attribute this to the fact that the process was more or less completed after four and one-half or five and one-half months.

On the basis of these studies I feel certain that the mechanism of decolorization is brought about by the action of leukocytes on the bile pigment.

To understand properly the pathogenesis of white bile one must first know the normal physiologic mechanisms at work in the gallbladder and bile ducts. The studies of Kausch and his successors are significant in this regard. According to these authors, bile is a mixture of secretions from the liver and the bile ducts. If the secretion from the liver should suddenly stop, one would expect to find the bile ducts filled with a colorless fluid which, without any doubt, would be a secretion of the ducts. Unfortunately, this cannot be proved in the experimental animal, because the hepatic secretion cannot be completely and suddenly cut off. Furthermore, even if this were possible, there would still remain a quantity of hepatic bile in the biliary system, and any fluid which was recovered would represent a mixture of the hepatic bile with the fluid produced by the ducts.

The methods used by Rous to prove the large quantity of fluid secreted by the ducts was double ligation of the ducts and aspiration of the secretion from the isolated portion. It seems doubtful to me, however, whether the enormous secretion obtained by Rous can really be considered as physiologic. It is easier to consider that the secretion was an abnormal one brought about by the double ligation, which acted at least as a mechanical, if not an infectious, stimulus for secretion.

Another fact of fundamental importance in the understanding of the physiologic processes involved is the concentrating effect of the gallbladder. This was well shown by Rous and McMaster, who introduced hepatic bile into the empty gallbladder of the living dog and recovered it from twelve to twenty-four hours later. The bile which they recovered was found to be much more concentrated than the original bile. It is evident from this that if the gallbladder is cut off from the liver-bile system, either anatomically or functionally, a less concentrated bile will be obtained.

Further data on the physiologic mechanisms involved can be obtained from the studies of Rous on white bile. I cannot concur with his con-

clusions completely, for reasons which will presently be given. Nevertheless, there remains much to make his work of physiologic importance.

In the first place, Rous assumed conditions to be simpler than those actually met in practice in that they are applicable only to the bile that is free from infection. Furthermore, the green system of Rous requires a gallbladder that is normal at least functionally. Considering the intimate relationship of all organs, it is difficult to imagine that ligation of the common duct does not have some effect on the normal functioning of the gallbladder.

If the gallbladder is to prevent the production of white bile by means of its concentrating effect, the hepatic bile, of course, must come into contact with the wall of the gallbladder. However, it is doubtful that this takes place in obstruction of the common duct. It is a common observation that during aspiration from the gallbladder or bile ducts there may be a change from a colorless to a colored fluid or vice versa. This indicates how little tendency there is for mixture of the contents of different parts of the biliary system.

In determining whether or not white bile will be formed, the concentrating and diluting effects of the gallbladder and ducts may be contributory but are certainly not the determining factors.

The decolorization responsible for the production of white bile is in all probability brought about by another factor, infection, and is merely increased or decreased by the action of the gallbladder and ducts. It would, of course, take a longer time for white bile to be produced in the green system than in the white system of Rous. The longest observation Rous made on any dog with the green system of Rous was for forty-four days. In my own experiments the shortest time for white bile to appear was in four and one-half months.

Thus, by a combination of the physiologic observations of Rous, Kausch and Bernhard and others and my own experimental results, I have arrived at the following conception of the manner in which white bile is produced:

In the closed system produced by obstruction a long-lasting infection of sufficient virulence produces a decolorization of the stagnant fluid in the gallbladder and bile ducts. It is the original green bile that is acted on and is directly responsible for the production of the colorless fluid. It is entirely possible that a small amount of secretion from the bile ducts may be mixed with this fluid, but in this closed system there certainly is not enough space for any great amount of such secretion to accumulate.

The gallbladder may play a great rôle in determining the time necessary for the decolorization to take place. A gallbladder that is func-

tionally intact and in complete connection with the duct system exerts a concentrating effect and thus lengthens the time necessary for the decolorizing process. On the other hand, if the gallbladder is separated from the duct system either anatomically or functionally, the decolorization will take place much sooner. It might be worth while to mention again at this point the fact that the foregoing considerations apply only to the colorless fluid found in the closed system.

Relief of Obstruction.—Relief of the obstruction immediately brings into play an entirely new set of circumstances. The next problem here is to investigate the colorless fluid often obtained from the common duct several days after relief of obstruction. As in the case of the closed system, one must determine the nature of the fluid obtained as well as its origin and the manner of its production.

In this connection it will be of special importance to understand the rôle played by the liver in producing white bile. The experimental work alone does not yield sufficient information on this point, since only the anatomic picture of the liver is available. No accurate correlation can be made between the anatomic appearance of the liver and its functional capacity. It is a well known observation that a liver with its parenchyma in poor anatomic condition may produce normal-appearing bile.

Another method of approach is the study of actual cases that have shown white bile in man, in which operation has brought about relief of obstruction and in which the resulting secretion is observed by means of a fistula for a definite period. Walters and Greene, as well as Andrews, have described a few such cases of relief of obstruction of the common duct. These authors agreed in reporting that after operation for obstruction the bile gradually changes from white to colored but that the immediate effect of the relief is the production of a greater quantity of white bile than was produced during the course of the obstruction. This cannot properly be called a colorless hepatic secretion, since the pigment content of the liver and the general jaundice present at this time bear witness to the fact that the hepatic cells are still producing bilirubin. Furthermore, one would hardly expect the character of the hepatic secretion to change from white to green within a short time. This change has often been observed to take place within a few hours, while in the case reported by Judd, mentioned previously, the bile changed from white to green immediately following the relief. It is probable that during the obstruction the bilirubin either is retained in the hepatic cells or is released into the blood stream. After relief of the obstruction this bilirubin might gradually make its way through the damaged biliary capillaries and produce a change to green bile.

COMMENT

Thus it seems that the secretion of the liver plays no part in the production of the colorless fluid drained from the common duct after relief of obstruction. There must be another origin for this fluid.

The only other possibility is that this fluid is a secretion of the mucous membrane of the ducts and is therefore very different from the colorless bile of the closed system. Unfortunately, this cannot be proved chemically, since both mucus and leukocytes are found in each case. Mucous secretion from the glands of the bile ducts undoubtedly plays some rôle in the closed system, too, as mentioned previously. Relief of the obstruction simply allows this secretory process of the ducts to take place unopposedly. On the other hand, the operation for relief of obstruction may either act as an inflammatory stimulus to the mucous membrane of the ducts or cause the recurrence of an old inflammation. Either factor would produce an increased quantity of colorless secretion for a few days. This fluid gradually becomes colored as a result of the activity of the liver, which mixes its pigment with the colorless fluid.

SUMMARY

Eleven dogs were used for the experimental work, which consisted of ligation of the common duct followed four weeks later by injection of bacteria into the biliary system. This procedure resulted in the appearance of white bile in four dogs.

In comparing the cases in which white bile appeared with those in which the bile remained unchanged, it is seen that the fundamental factor in the pathogenesis of white bile is the presence of infection. Infection accompanying obstruction of the common duct must be present for a long time and must be of sufficient virulence. The beginning of decolorization was demonstrated after thirty-two days, while completely white bile appeared after four and one-half months. The most effective organism for bringing about this infection seems to be B. coli.

In discussing the pathogenesis of white bile a sharp distinction is made between white bile found in the closed biliary system and the colorless fluid obtained from the open system after relief of obstruction.

In the closed system infection brings about a transition of the originally green bile to white bile. This decolorization is brought about by the leukocytes, which appear as a result of the bacterial stimulus. They absorb the bile pigment and carry it off. A small amount of secretion from the mucous membrane of the ducts is subsequently mixed with this colorless fluid. Quantatively, however, this plays a minor rôle.

As a result of the relief of obstruction the white bile is swept out of the bile ducts. For a few days an increased quantity of colorless fluid is obtained, which is shown to be the secretion of the mucous mem-

brane of the ducts. Since this secretion has nothing to do with hepatic bile, to apply to it the name of white bile would be misleading. Here again infection seems to play some part in the production of the colorless fluid. It is highly probable that the operation for relief of obstruction causes an increased secretion by acting as an inflammatory stimulus to the mucous membrane of the ducts. Gradually the liver assumes its normal function, if it has not been too severely damaged anatomically.

In addition, there are reported four clinical cases in which white bile was found, these constituting 15 per cent of the total number (twenty-six) of cases in which operation for obstruction of the common duct was performed at the University of Chicago Clinics during the last five years. This relatively high percentage can be explained by the fact that these statistics include cases in which the presence of white bile was discovered only on chemical examination. In these four cases the clinical history, the findings at operations and in one case the post-mortem examination revealed signs of long-lasting infection accompanying obstruction of the common duct. Two cases of long-lasting obstruction of the common duct are reported in which neither clinically nor at operation were there any signs of infection. In both cases deep green bile was obtained.

The histories of the clinical cases reported agree with the histories cited in the American literature in indicating the prognosis in cases of white bile to be serious but not hopeless.

THE SO-CALLED "LIVER DEATH"

AN EXPERIMENTAL STUDY OF CHANGES IN THE BILIARY DUCTS FOLLOWING DECOMPRESSION OF THE OBSTRUCTED BILIARY TREE

FREDERICK FITZHERBERT BOYCE, M.D.

AND

ELIZABETH M. McFETRIDGE, M.A.

NEW ORLEANS

In previous communications on this subject[1] we have discussed two separate phases of the so-called "liver death" or "liver-kidney syndrome."

We have analyzed thirty-four cases of this syndrome described in the records of the New Orleans Charity Hospital in the seven year period terminating on Dec. 31, 1934. In twenty-three cases the syndrome followed operation on the biliary tract; in four it followed surgical treatment for acute pancreatitis, and in seven it was associated with trauma to the liver.

We have reported a series of experiments, ten in all, in which we endeavored to reproduce in laboratory animals the clinical and pathologic processes which we had observed in human patients. Two experiments were successful:

In the first experiment, the biliary tree was obstructed for from twelve to twenty days (by ligation and division of the common bile duct and cholecystectomy), at the end of which time the obstruction was released and an external biliary fistula was created. In every instance after the decompression there was a prompt decrease in the jaundice, followed almost immediately by increasing listlessness, anorexia without gastro-intestinal symptoms, and oliguria which rapidly progressed to anuria. Death occurred in from seventy-two to ninety-six hours in all the animals which were not killed when their state was clearly terminal. Urinalysis showed albumin, casts and red blood cells, and in five instances the previously normal nonprotein nitrogen content of the blood rose to 72, 81, 93, 105 and 171 mg., respectively. In all the dogs autopsy showed degenerative changes in the liver cells and in the convoluted tubules of the kidneys typical of the lesions exhibited in cases of liver-kidney death in human patients.

From the Department of Surgery of the School of Medicine of Louisiana State University.

1. Boyce, F. F., and McFetridge, E. M.: So-Called "Liver Death": A Clinical and Experimental Study, Arch. Surg. **31**:105 (July) 1935. "Liver Deaths" in Surgery: Analysis of Thirty-Four Cases, New Orleans M. & S. J. **88**:563 (March) 1936. Boyce, F. F.: An Experimental Study of the So-Called Liver Death Syndrome in Biliary Surgery, Proc. Soc. Exper. Biol. & Med. **32**:479, 1934.

In the second experiment, precisely similar clinical symptoms and postmortem hepatorenal changes followed the injection into the animals of saline and aqueous extracts made from the liver of a patient who died with the typical syndrome of hyperpyrexia characteristic of liver death after cholecystectomy; the alcoholic extract did not reproduce the picture. Autopsy on this patient had ruled out hemorrhage, leakage of bile, peritonitis, embolism and pneumonia and had revealed marked necrosis of the liver cells. The urine of these animals revealed albumin, casts and red blood cells, but determinations of the chemical composition of the blood, unfortunately, were not made, since the experiment was one of the first done and its full significance was not realized.

On the basis of this clinical and experimental evidence, we have evolved the following theory to explain the occurrence of this highly fatal complication:

1. The same symptom complex is apparent and the same underlying factors are operative in the various conditions studied (postoperative biliary disease, postoperative pancreatic disease and hepatic trauma), and we believe, on the basis of a casual survey of unselected autopsy reports in cases of disease of the thyroid gland, burns and intestinal obstruction, that this same syndrome may develop in these and perhaps in other pathologic states in which it has not yet been identified.

2. The underlying factor is some degree of hepatic damage which either is preexistent or is the result of direct trauma. In the former circumstances the damage is not incompatible with the strain of normal life, but it is incompatible with the added strain incident to surgical intervention. The chain of events following hepatic trauma is the same, except that the damage is abruptly produced and is not of gradual development as it is in diseased states.

3. When such a strain is superimposed on the existing hepatic disability, the damaged liver cells, failing in their function, release into the circulation some potent toxic substance, which, on the basis of our experimental evidence, seems to be water soluble.

4. This substance, circulating in the blood, is excreted by the kidneys through the convoluted tubules, and they, unfitted by nature for such a load, promptly break under it.

5. The two types of liver death originally described by Charles Gordon Heyd [2] we consider to be a single pathologic process. Our evidence indicates that cases in which sudden death occurs with hyperpyrexia and in which only hepatic changes are apparent at autopsy represent the first stage of the process which terminates in deferred death from uremia, in which renal as well as hepatic changes are apparent at autopsy.

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2. Heyd, C. F.: Liver and Its Relation to Chronic Abdominal Infection, Ann. Surg. **79**:55 (Jan.) 1924.

The clinical and experimental evidence which we ourselves have adduced corroborates the suggestion made by other writers on the subject, notably Helwig, Schutz and Kuhn,[3] that the toxin postulated in our theory is produced in the liver cells, in which, it is generally agreed, the first damage occurs.

Both positive and negative proof is necessary to establish this theory. On the positive side, the toxic substance must be isolated from the damaged liver cells, and this we are attempting to do at the time of writing. On the negative side, it must be proved that it does not originate elsewhere in the biliary system, and with that proof this communication is concerned.

If the toxin in question should be produced anywhere in the biliary system except in the damaged liver cells, the most reasonable place would be the tissues lining the biliary ducts. These ducts, especially if

TABLE 1.—*Results of Simple Obstruction of the Biliary Tree in Six Dogs, Which Were Used as Controls*

Dog	Procedure	Duration of Obstruction, Days	Observations
9	Ligation and division of the common duct	4	Not significant
14	Ligation and division of the common duct; cholecystectomy	6	Not significant
16	Ligation and division of the common duct; cholecystectomy	18	Very slight flattening of the epithelial cells lining the small and medium-sized ducts
17	Ligation and division of the common duct; cholecystectomy	20	Not significant
18	Ligation and division of the common duct; cholecystectomy	20	Not significant
4	Ligation and division of the common duct	36	Slight flattening of the epithelial cells, as in dog 16

the gallbladder has been removed, are the only structures other than the liver cells which feel the effect of biliary stasis. In order to make certain that they are not implicated in the production of the toxic substance, we undertook a series of experiments in which we studied the effect on them of decompression after obstruction and in which we studied, as a control, the effect on them of simple obstruction.

Our report, after the elimination of the dogs which died of infection and of other causes after experimental obstruction of the biliary tree, concerns twelve dogs. In six animals, which were used as controls, obstruction was done and was not released; in the other six decompression of the obstruction was done from four to thirty-six days after the obstruction had been produced.

3. Helwig, F., and Schutz, C. B.: A Liver Kidney Syndrome, Surg., Gynec. & Obst. **55**:570 (Nov.) 1932. Schutz, C. B.; Helwig, F. C., and Kuhn, H. P.: A Contribution to the Study of So-Called Liver Death, J. A. M. A. **99**:633 (Aug. 20) 1932.

With the animal under light ether anesthesia, the common duct was tightly ligated and then divided within a half-inch of its entrance into the duodenum. In four of the control dogs and in one of the others the gallbladder was removed at the same time.

At intervals of from four to thirty-six days after the original operation the obstruction was released in six dogs, under the same type of anesthesia and through the same scar. Cholecystectomy or choledochostomy was done, according to whether or not the gallbladder had been removed. The dogs were then killed after various intervals, as the tables show. In the case of the single dog which died of natural causes after the second operation autopsy was performed within an hour after its death.

Clinically the result of the experimental obstruction was the same in all the animals. Jaundice developed in all, the degree depending on the duration of the obstruction, and all exhibited varying degrees of anorexia, listlessness and

TABLE 2.—*Experimental Findings on Six Dogs in Which Decompression Was Done*

Dog	Procedure	Duration of Obstruction, Days	Duration of Decompression	Observations
10	Ligation and division of the common duct; cholecystostomy	4	3⅛ days	Not significant
15	Ligation and division of the common duct, cholecystectomy; choledochostomy	7	2½ hours	Not significant
12	Ligation and division of the common duct; cholecystostomy	14	6 days	Not significant
6	Ligation and division of the common duct; cholecystostomy	14	7 days	Natural death, immediate autopsy; multiple hepatic abscesses; no change in the biliary ducts
13	Ligation and division of the common duct; cholecystostomy	20	4 days	Columnar type of epithelium in lining cells of small and medium-sized ducts
5	Ligation and division of the common duct; cholecystostomy	36	4 days	Columnar type of epithelium as in dog 13; marked fatty change in central area of lobulus

loss of weight. The highest icteric index was 120, but further laboratory studies showed no other significant changes except the appearance of bile in the urine.

At the second operation exploration revealed no free fluid in the abdominal cavity or any other evidence of infection. Whenever the gallbladder was still present, it was markedly distended, as was the whole extrahepatic biliary tree. The tension in the bile ducts, particularly in the common bile duct, was naturally much greater when the gallbladder was not in situ. The bile in all instances was thick and black. The degree of jaundice in the tissues varied with the duration of the obstruction, as did the size and color of the liver, which was always enlarged and dark green.

The immediate flow of bile through the catheter inserted into the gallbladder or the common bile duct and the continued drainage of bile through it until death made it clear that the obstruction had been completely released. In two animals the tube was clamped off at intervals and was later released, but this variation of the usual procedure produced no significant change in the chemical composition of the blood or in the urine.

The animals in which simple obstruction had been done were killed in from four to thirty-six days; the animals in which subsequent decompression was done were killed in from two and one-half hours to seven days. In no instance was there any evidence of peritonitis, and the observations at autopsy on the control group paralleled the observations on the other group at the second operation, when decompression had been done. In all the dogs in which decompression had been done the liver had decreased in size and the jaundice had decreased in degree. The only notable gross changes were in dog 6, in which the liver was studded with small abscesses seven days after decompression, and in dog 13, in which the liver was peculiarly soft and friable four days after decompression.

Histologic study of sections of the livers of both groups of dogs showed various degrees of necrotic change in the liver cells, especially those in the inner third of the lobule and about the large bile ducts. In no instance, however, did it approach the degree of necrosis noted in either the clinical or the experimental cases of "liver death" studied in our first report. The less marked character of the necrotic change is easily explained: The dogs in which obstruction was continued longest in this group of experiments did not have their gallbladders removed, as did the dogs in which necrotic changes were observed in our first series of experiments.

These necrotic changes are purely mechanical and are the direct result of the increase in the intrahepatic pressure which follows experimental obstruction of the bile duct. When the gallbladder is in situ, it serves as a sort of buffer, in that it absorbs and concentrates the bile, thus reducing it in quantity, and it acts also as a reservoir for bile. As a consequence, the rise in intraductal pressure, as well as the subsequent rise in intrahepatic pressure, is more gradual than is the rise in pressure when the gallbladder has been removed. When cholecystectomy has been done in addition, the intrahepatic ducts and the intraductal hepatic system in turn become enormously dilated as bile accumulates and biliary stasis increases. The pressure in the intrahepatic vascular tree must rise correspondingly to permit the liver cells to function at all, and it is a physical phenomenon that the cells first become atrophied and then, as the pressure increases, exhibit all gradations of change from simple degeneration to actual necrosis. That, if we may so express it, is the normal pathologic picture that follows biliary stasis.

When the biliary obstruction is released, on the other hand, and particularly when it is abruptly released, the first consequence is a reactionary hyperemia. The second consequence is a still more marked necrosis of the liver cells, from which, as the blood supply in them increases, the products of the necrotic change are swept out into the circulation, just as we have postulated in the theory we have advanced.

Since such changes take place in the liver cells, it might be assumed that similar changes would take place in the bile ducts and that their lining cells would show, first of all, some degree of flattening. In only

four of the experimental animals was any change noted in these cells, but in all of them it was of this sort. In dog 16, in which the bile duct had been obstructed for eighteen days, there was noted a slight degree of flattening of these cells. In dog 4, in which the bile duct had been obstructed for thirty-six days, more marked changes of the same sort were noted. In dog 5, in which the bile duct had been obstructed for thirty-six days and decompressed for four days, and in dog 13, in which the bile duct had been obstructed for twenty days and decompressed for four days, it was observed that the cells were of the columnar type, which seemed to suggest that they had been flattened but that they were springing back to their normal state. All the changes were noted in the small and medium-sized ducts. The epithelium of the large ducts showed no change.

Histologic study of sections of the liver showed in all instances the usual reaction of round cell infiltration and of polymorphonuclear cells. These changes, however, are not peculiar to either biliary stasis or its release.

These negative histologic observations may be interpreted to indicate that the lining cells of the biliary tree play no part in the production of the liver-kidney syndrome. Indeed, if our theory be correct, that this syndrome is apparent in other pathologic states as well as in disease of the biliary tract, it is scarcely reasonable to suppose that they could play any part, since the ductal system of the biliary tract is not concerned in these other conditions. The absence of positive findings in the lining cells of the biliary ducts seems to us another link in the chain of evidence pointing to the liver cells as the source of the lethal toxin in the liver-kidney syndrome.

In view of our own negative results in these experiments, it was at first rather disconcerting to find exactly reverse results reported by Stewart and Cantarow [4] in a somewhat similar series of experiments on nineteen cats. Experimental obstruction was continued in these animals for from one to sixteen days and was followed by decompression for from one hour to seven days. The principal changes which they noted were:

1. A progressive proliferation of the cells of the mucosa and of the cells lining the biliary ducts followed obstruction and finally amounted to papillary and adenomatous changes.

2. Mitosis and budding of the cells in the smaller ducts were present as early as twenty-four hours after obstruction had been done. In the small and the medium-sized ducts the enlargement of the epithelial and infiltrating cells was at times so marked as to occlude the lumen completely.

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4. Stewart, H. L., and Cantarow, A.: Decompression of the Obstructed Biliary System of the Cat, Am. J. Digest. Dis. & Nutrition **2**:101 (April) 1935.

3. Necrosis of the adenomatous processes in the mucosa of the large ducts occurred as early as an hour and a half after decompression, the regressive changes becoming more marked as time went on.

4. Atrophy and final disappearance of the newly proliferated ducts occurred as the result of regeneration of the hepatic cells.

The necrotic changes in the liver cells reported by Stewart and Cantarow were duplicated in our own experiments, but their other findings were not, and the discrepancy was at first disconcerting. Second thought, however, gave us the explanation: In our experiments the obstruction was released by the creation of an external biliary fistula, which is analogous, it should be noted, to the procedure that would be carried out clinically. In their experiments, on the other hand, the obstruction was released merely by the release of the ligature on the common bile duct, which had not been divided, as it had been in our experiments. The type of procedure that they employed does not reproduce the clinical and pathologic conditions usually found, and the changes which followed it, therefore, would scarcely be observed after a different type of operation.

We made no observations of the kidneys in this series of experiments. Previous clinical and experimental studies have convinced us that the renal changes are the second stage of the syndrome. Since even the first stage was not produced in these experiments, there seemed to us to be small point in wasting time seeking for the second.

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